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 NEWS  4  OCT 07   Multiple databases enhanced for more flexible patent
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 NEWS  5  OCT 22   Current-awareness alert (SDI) setup and editing
                   enhanced
 NEWS  6  OCT 22   WPIDS, WPINDEX, and WPIX enhanced with Canadian PCT
                   Applications
 NEWS  7  OCT 24   CHEMLIST enhanced with intermediate list of
                   pre-registered REACH substances
 NEWS  8  NOV 21   CAS patent coverage to include exemplified prophetic
                   substances identified in English-, French-, German-,
                   and Japanese-language basic patents from 2004-present
 NEWS  9  NOV 26   MARPAT enhanced with FSORT command
 NEWS 10  NOV 26   MEDLINE year-end processing temporarily halts
                   availability of new fully-indexed citations
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L1            0 CELL(W) FREE AND (EGL(W) 30 OR EGL(W) 3 OR EGL(W) 8 OR RIC(W)
                8)

=> s cell(w)free and (guanine(w)nucleotide(w)binding(w)protein)
L2          515 CELL(W) FREE AND (GUANINE(W) NUCLEOTIDE(W) BINDING(W) PROTEIN)

=> s l2 and inhibit
L3           72 L2 AND INHIBIT

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4            52 DUP REM L3 (20 DUPLICATES REMOVED)

=> dis ibib abs l4 1-52

L4   ANSWER 1 OF 52  CAPLUS  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:         2008:535795  CAPLUS
DOCUMENT NUMBER:          148:531875
TITLE:                    Identification of a Conserved Rac-binding Site on
                          NADPH Oxidases Supports a Direct GTPase Regulatory
                          Mechanism
AUTHOR(S):                Kao, Yu-Ya; Gianni, Davide; Bohl, Benjamin; Taylor,
                          Ross M.; Bokoch, Gary M.
CORPORATE SOURCE:         Departments of Immunology and Cell Biology, The
                          Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE:                   Journal of Biological Chemistry (2008), 283(19),
                          12736-12746
                          CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER:                American Society for Biochemistry and Molecular
                          Biology
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The NADPH oxidases (Noxs) are a family of superoxide-generating enzymes
     implicated in a variety of biol. processes.  Full activity of Nox1, -2,
     and -3 requires the action of a Rac GTPase.  A direct regulatory
     interaction of Rac with Nox2 has been proposed as part of a two-step
     mechanism for regulating electron transfer during superoxide formation.
     Using truncation anal. of Rac binding to the cytoplasmic tail of Nox2,
     along with peptides derived from this region in cell-
     free assays, we identify a Rac interaction site within amino acids
     419-430 of Nox2.  This region is required for binding Rac2 but not p47phox
     or p67phox cytosolic regulatory factors.  A cell-permeant version of the
     peptide encompassing amino acids 419-430 specifically inhibits
     NADPH oxidase activation in intact human neutrophils.  Mutational anal. of
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the putative Rac-binding site revealed specific residues, particularly Lys-421, Tyr-425, and Lys-426, individually required for Rac-dependent NADPH oxidase activity that are conserved in the Rac-regulated Nox1, Nox2, and Nox3 enzymes but not in Nox4 or Nox5. Mutation of the conserved residues in the Rac-binding site of Nox1 also result in the loss of Rac-dependent activity. Our data identify a functional Rac interaction site conserved in Rac-dependent Noxs and support a direct regulatory interaction of Rac GTPases to promote activation of these NADPH oxidases.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2008:99000 CAPLUS
DOCUMENT NUMBER: 148:165961
TITLE: The Parkinson's disease protein α-synuclein disrupts cellular Rab homeostasis
AUTHOR(S): Gitler, Aaron D.; Bevis, Brooke J.; Shorter, James; Strathearn, Katherine E.; Hamamichi, Shusei; Su, Linhui Julie; Caldwell, Kim A.; Caldwell, Guy A.; Rochet, Jean-Christophe; McCaffery, J. Michael; Barlowe, Charles; Lindquist, Susan
CORPORATE SOURCE: Whitehead Institute for Biomedical Research, Howard Hughes Medical Institute, Cambridge, MA, 02142, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2008), 105(1), 145-150
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB α-Synuclein (α-syn), a protein of unknown function, is the most abundant protein in Lewy bodies, the histol. hallmark of Parkinson's disease (PD). In yeast, α-syn inhibits endoplasmic reticulum (ER)-to-Golgi (ER → Golgi) vesicle trafficking, which is rescued by overexpression of a Rab GTPase that regulates ER → Golgi trafficking. The homologous Rab1 rescues α-syn toxicity in dopaminergic neuronal models of PD. Here, the authors investigated this conserved feature of α-syn pathobiol. In a cell-free system with purified transport factors, α-syn inhibited ER → Golgi trafficking in an α-syn dose-dependent manner. Vesicles budded efficiently from the ER, but their docking or fusion to Golgi membranes was inhibited. Thus, the in vivo trafficking problem is due to a direct effect of α-syn on the transport machinery. By ultrastructural anal., the earliest in vivo defect was an accumulation of morphol. undocked vesicles, starting near the plasma membrane and growing into massive intracellular vesicular clusters in a dose-dependent manner. By immunofluorescence/immunoelectron microscopy, these clusters were associated both with α-syn and with diverse vesicle markers, suggesting that α-syn can impair multiple trafficking steps. Other Rabs did not ameliorate α-syn toxicity in yeast, but RAB3A, which is highly expressed in neurons and localized to presynaptic termini, and RAB8A, which is localized to post-Golgi vesicles, suppressed toxicity in neuronal models of PD. Thus, α-syn causes general defects in vesicle trafficking, to which dopaminergic neurons are especially sensitive.
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2006:459789 CAPLUS
DOCUMENT NUMBER: 145:41967
TITLE: Inhibition of a background potassium channel by Gq protein α-subunits
AUTHOR(S): Chen, Xiangdong; Talley, Edmund M.; Patel, Nitin;

Gomis, Ana; McIntire, William E.; Dong, Biwei; Viana, Felix; Garrison, James C.; Bayliss, Douglas A.

CORPORATE SOURCE: Department of Pharmacology, University of Virginia, Charlottesville, VA, 22908, USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2006), 103(9), 3422-3427
CODEN: PNASA6; ISSN: 0027-8424

PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Two-pore-domain K+ channels provide neuronal background currents that establish resting membrane potential and input resistance; their modulation provides a prevalent mechanism for regulating cellular excitability. The so-called TASK channel subunits (TASK-1 and TASK-3) are widely expressed, and they are robustly inhibited by receptors that signal through Gαq family proteins. Here, we manipulated G protein expression and membrane phosphatidylinositol 4,5-bisphosphate (PIP2) levels in intact and cell-free systems to provide electrophysiol. and biochem. evidence that inhibition of TASK channels by Gαq-linked receptors proceeds unabated in the absence of phospholipase C (PLC) activity, and instead involves association of activated Gαq subunits with the channels. Receptor-mediated inhibition of TASK channels was faster and less sensitive to a PLCβ1-ct minigene construct than inhibition of PIP2-sensitive Kir3.4(S143T) homomeric channels that is known to be dependent on PLC. TASK channels were strongly inhibited by constitutively active Gαq, even by a mutated version that is deficient in PLC activation. Receptor-mediated TASK channel inhibition required exogenous Gαq expression in fibroblasts derived from Gαq/11 knockout mice, but proceeded unabated in a cell line in which PIP2 levels were reduced by regulated overexpression of a lipid phosphatase. Direct application of activated Gαq, but not other G protein subunits, inhibited TASK channels in excised patches, and constitutively active Gαq subunits were selectively coimmunopptd. with TASK channels. These data indicate that receptor-mediated TASK channel inhibition is independent of PIP2 depletion, and they suggest a mechanism whereby channel modulation by Gαq occurs through direct interaction with the ion channel or a closely associated intermediary.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 52 EMBASE

ACCESSION NUMBER: 2004118491 EMBASE

TITLE: Ceramide inhibition of phospholipase D and its relationship to RhoA and ARF1 translocation in GTPγS-stimulated polymorphonuclear leukocytes.

AUTHOR: Boxer, Laurence A. (correspondence)

CORPORATE SOURCE: University of Michigan, Department of Pediatrics, L2110 Women's Hospital, 1500 E Medical Center Dr, Ann Arbor, MI 48109, United States. laboxer@med.umich.edu

AUTHOR: Mansfield, Parnela J.; Carey, Shannon S.; Hinkovska-Galcheva, Vania; Shayman, James A.

SOURCE: Blood, (15 Mar 2004) Vol. 103, No. 6, pp. 2363-2368.
Refs: 36
ISSN: 0006-4971 CODEN: BLOOAW

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 025 Hematology
029 Clinical and Experimental Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 12 Apr 2004

Last Updated on STN: 12 Apr 2004

AB Phospholipase D (PLD) regulates the polymorphonuclear leukocyte (PMN) functions of phagocytosis, degranulation, and oxidant production. Ceramide inhibition of PLD suppresses PMN function. In streptolysin O-permeabilized PMNs, PLD was directly activated by guanosine 5'-[gamma-thio]triphosphate (GTPγS) stimulation of adenosine diphosphate (ADP)-ribosylation factor (ARF) and Rho, stimulating release of lactoferrin from specific granules of permeabilized PMNs; PLD activation and degranulation were inhibited by C (2)-ceramide but not dihydro-C(2)-ceramide. To investigate the mechanism of ceramide's inhibitory effect on PLD, we used a cell-free system to examine PLD activity and translocation from cytosol to plasma membrane of ARF, protein kinase C (PKC)α and β, and RhoA, all of which can activate PLD. GTPγS-activated cytosol stimulated PLD activity and translocation of ARF, PKCα and β, and RhoA when recombined with cell membranes. Prior incubation of PMNs with 10 μM C(2)-ceramide inhibited PLD activity and RhoA translocation, but not ARF1, ARF6, PKCα, or PKCβ translocation. However, in intact PMNs stimulated with N-formyl-1-methionyl-1-leucyl-1-phenylalamine (FMLP) or permeabilized PMNs stimulated with GTPγS, C(2)-ceramide did not inhibit RhoA translocation. Exogenous RhoA did not restore ceramide-inhibited PLD activity but bound to membranes despite ceramide treatment. These observations suggest that, although ceramide may affect RhoA in some systems, ceramide inhibits PLD through another mechanism, perhaps related to the ability of ceramide to inhibit phosphatidylinositol-bisphosphate (PIP(2)) interaction with PLD.

L4 ANSWER 5 OF 52 CAPLUS

ACCESSION NUMBER: 2003:22597 CAPLUS
DOCUMENT NUMBER: 138:85352
TITLE: T1R hetero-oligomeric taste receptors and use thereof for identification of taste compounds
INVENTOR(S): Zoller, Mark T.; Li, Xiaodong; Staszewski, Lena; O'Connell, Shawn; Zozulya, Sergey; Adler, Joan Elliott; Xu, Hong; Echeverri, Fernando
PATENT ASSIGNEE(S): Senomyx, Inc., USA
SOURCE: PCT Int. Appl., 135 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003001876	A2	20030109	WO 2002-US19970	20020626
WO 2003001876	A3	20031204		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 20020160424	A1	20021031	US 2001-897427	20010703
US 6955887	B2	20051018		
US 20030054448	A1	20030320	US 2002-35045	20020103
US 7241880	B2	20070710		

CA 2451317	A1	20030109	CA 2002-2451317		20020626
AU 2002326315	A1	20030303	AU 2002-326315		20020626
AU 2002326315	B2	20070705			
EP 1412750	A2	20040428	EP 2002-761016		20020626
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR					
JP 2005500318	T	20050106	JP 2003-508132		20020626
US 20030220479	A1	20031127	US 2002-318031		20021213
US 7208290	B2	20070424			
US 20040209286	A1	20041021	US 2003-725276		20031202
US 20050032158	A1	20050210	US 2003-725284		20031202
US 7435552	B2	20081014			
MX 2003PA11410	A	20040630	MX 2003-PA11410		20031209
NO 2003005761	A	20040220	NO 2003-5761		20031222
US 20070292944	A1	20071220	US 2007-745857		20070508
AU 2007203680	A1	20070823	AU 2007-203680		20070807
US 20080214784	A1	20080904	US 2007-877158		20071023
US 20080220451	A1	20080911	US 2007-877138		20071023
PRIORITY APPLN. INFO.:			US 2001-300434P	P	20010626
			US 2001-897427	A	20010703
			US 2001-304749P	P	20010713
			US 2001-310493P	P	20010808
			US 2001-331771P	P	20011121
			US 2001-339472P	P	20011214
			US 2002-35045	A	20020103
			US 2002-372090P	P	20020415
			US 2002-374143P	P	20020422
			US 2002-374522P	P	20020423
			US 2001-259227P	P	20010103
			US 2001-284547P	P	20010419
			AU 2002-326315	A3	20020626
			WO 2002-US19970	W	20020626
			US 2007-745857	A3	20070508

AB The present invention relates to the discovery that the T1R receptors assemble to form functional taste receptors. Particularly, it has been discovered that co-expression of T1R1 and T1R3 results in a taste receptor that responds to umami taste stimuli, including monosodium glutamate. Also, it has been discovered that co-expression of the T1R2 and T1R3 receptors results in a taste receptor that responds to sweet taste stimuli including naturally occurring and artificial sweeteners. Also the present invention relates to the use of hetero-oligomeric taste receptors comprising T1R1/T1R3 and T1R2/T1R3 in assays to identify compds. that resp. respond to umami taste stimuli and sweet taste stimuli. Further, the invention relates to the constitutive of cell lines that stably or transiently co-express a combination of T1R1 and T1R3; or T1R2 and T1R3; under constitutive or inducible conditions. The use of these cells lines in cell-based assays to identify umami and sweet taste modulatory compds. is also provided, particularly high throughput screening assays that detect receptor activity by use of fluorometric imaging. Finally, the invention relates to the discovery that some compds., e.g., lactisole, inhibit both the activities of human T1R2/T1R3 and T1R1/T1R3 receptors, and accordingly the sweet and umami taste, suggesting that these receptors may be the only sweet and umami receptors. Examples of the invention show protein sequence alignments of human and rat T1R taste receptors, mRNA expression of human T1R2 and T1R3 receptors in tongue tissue, and functional data for the human T1R taste receptors.

L4 ANSWER 6 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:995084 CAPLUS
DOCUMENT NUMBER: 140:124154
TITLE: Intra-Golgi Protein Transport Depends on a Cholesterol Balance in the Lipid Membrane

AUTHOR(S): Stueven, Ernstpeter; Porat, Amir; Shimron, Frida; Fass, Ephraim; Kaloyanova, Dora; Bruegger, Britta; Wieland, Felix T.; Elazar, Zvulun; Helms, J. Bernd
CORPORATE SOURCE: Biochemie-Zentrum Heidelberg, University of Heidelberg, Heidelberg, 69120, Germany
SOURCE: Journal of Biological Chemistry (2003), 278(52), 53112-53122
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transport of proteins between intracellular membrane compartments is mediated by a protein machinery that regulates the budding and fusion processes of individual transport steps. Although the core proteins of both processes are defined at great detail, much less is known about the involvement of lipids. Here we report that changing the cellular balance of cholesterol resulted in changes of the morphol. of the Golgi apparatus, accompanied by an inhibition of protein transport. By using a well characterized cell-free intra-Golgi transport assay, these observations were further investigated, and it was found that the transport reaction is sensitive to small changes in the cholesterol content of Golgi membranes. Addition as well as removal of cholesterol (10 ± 6%) to Golgi membranes by use of methyl-β-cyclodextrin specifically inhibited the intra-Golgi transport assay. Transport inhibition occurred at the fusion step. Modulation of the cholesterol content changed the lipid raft partitioning of phosphatidylcholine and heterotrimeric G proteins, but not of other (non) lipid raft proteins and lipids. We suggest that the cholesterol balance in Golgi membranes plays an essential role in intra-Golgi protein transport and needs to be carefully regulated to maintain the structural and functional organization of the Golgi apparatus

REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2003:676656 CAPLUS
DOCUMENT NUMBER: 139:320546
TITLE: Receptor activation regulates cortical, but not vesicular localization of NDP kinase
AUTHOR(S): Gallagher, Betty C.; Parrott, Kimberly A.; Szabo, Gabor; Otero, Angela de S.
CORPORATE SOURCE: Department of Molecular Physiology and Biological Physics, University of Virginia Medical School, Charlottesville, VA, 22908, USA
SOURCE: Journal of Cell Science (2003), 116(15), 3239-3250
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We used immunofluorescence techniques to determine the localization of nucleoside diphosphate (NDP) kinase in NIH-3T3 fibroblasts. We found that cytoplasmic NDP kinase can be separated into two populations according to subcellular localization and response to extracellular stimuli. Specifically, within minutes of stimulation of resting fibroblasts with serum, growth factors or bombesin, a portion of NDP kinase becomes associated with membrane ruffles and lamellipodia. Another pool of NDP kinase accumulates independently of stimulation around intracellular vesicles. Transfection of cells with activated Rac mimics, whereas expression of dominant neg. Rac inhibits, the effects of extracellular stimulation on the translocation of NDP kinase to the cell cortex. Neither Rac mutant affects the vesicle-associated pool. Association of NDP

kinase with vesicles depends on microtubule integrity and is disrupted by nocodazole. In cell-free assays NDP kinase binds tightly to membrane vesicles associated with taxol-stabilized microtubules. Binding of NDP kinase to this fraction is reduced by ATP and abolished by GTP, as well as guanine nucleotides that are NDP kinase substrates. Thus, the localization of the two NDP kinase pools identified here is regulated independently by distinct cellular components: the appearance of cortical NDP kinase is a consequence of Rac activation, whereas vesicular NDP kinase is responsive to microtubule dynamics and nucleotides, in particular GTP. These results suggest that in fibroblasts NDP kinase participates in Rac-related cortical events and in GTP-dependent processes linked to intracellular vesicle trafficking.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:314918 CAPLUS

DOCUMENT NUMBER: 139:65093

TITLE: Golgin-84 is a rab1 binding partner involved in Golgi structure

AUTHOR(S): Satoh, Ayano; Wang, Yanzhuang; Malsam, Jorg; Beard, Matthew B.; Warren, Graham

CORPORATE SOURCE: Department of Cell Biology, Yale University School of Medicine, New Haven, CT, 06520-8002, USA

SOURCE: Traffic (Oxford, United Kingdom) (2003), 4(3), 153-161
CODEN: TRAFFA; ISSN: 1398-9219

PUBLISHER: Blackwell Munksgaard

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Members of the golgin family of coiled-coil proteins have been implicated in the tethering of vesicles to Golgi membranes and cisternal membranes to each other. Many also bind to rab GTPases. Golgin-84 is a membrane-anchored golgin that we now show binds preferentially to the GTP form of the rab1 GTPase. It is also present throughout the Golgi stack by immuno-EM. Antibodies to golgin-84 inhibit stacking of cisternal membranes in a cell-free assay for Golgi reassembly, whereas the cytoplasmic domain of golgin-84 stimulates stacking and increases the length of re-assembled stacks. Transient expression of golgin-84 in NRK cells helps prevent the disassembly of the Golgi apparatus normally triggered by treatment with brefeldin A. Together these data suggest that golgin-84 is involved in generating and maintaining the architecture of the Golgi apparatus

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2003:398127 CAPLUS

DOCUMENT NUMBER: 140:195258

TITLE: Two Pathways of Activation of the Superoxide-Generating NADPH Oxidase of Phagocytes in vitro-Distinctive Effects of Inhibitors

AUTHOR(S): Sigal, Natalia; Gorzalczany, Yara; Pick, Edgar

CORPORATE SOURCE: Department of Human Microbiology, Tel Aviv University, Tel Aviv-Jaffa, 69978, Israel

SOURCE: Inflammation (Dordrecht, Netherlands) (2003), 27(3), 147-159
CODEN: INFLD4; ISSN: 0360-3997

PUBLISHER: Kluwer Academic Publishers

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The NADPH oxidase complex of phagocytes comprises a membrane-associated flavocytochrome b559, and 4 cytosolic components: p47phox, p67phox,

p40phox, and the small GTPase Rac. Activation of the oxidase in vivo is the result of assembly of the cytosolic components with cytochrome b559 and is mimicked in vitro by a cell-free system consisting of membranes, p47phox, p67phox, non-prenylated or prenylated Rac, and an anionic amphiphile as activator (defined as "p47phox and amphiphile-dependent" or canonical pathway). We reported that prenylated Rac1 is capable of activating the NADPH oxidase in vitro in the absence of p47phox and amphiphile (defined as "p47phox and amphiphile-independent" pathway). We now demonstrate that the 2 pathways exhibit distinctive susceptibilities to inhibitors: (1) The anionic amphiphile lithium dodecyl sulfate, an activator of the canonical pathway, has the opposite effect (inhibition) on oxidase activation by prenylated Rac and p67phox; (2) GDP and, paradoxically, GTP (but not GMP, ATP, ADP, and AMP) prevent oxidase activation by the p47phox and amphiphile-independent pathway but do not affect activation by the canonical pathway; (3) The Rac-binding domain of p21-activated kinase is a potent inhibitor of activation by the p47phox and amphiphile-independent pathway while exerting a milder inhibitory effect on the canonical pathway; (4) The C-terminal polybasic Rac1 peptide 177-191 and the cationic antibiotic neomycin sulfate inhibit activation by the canonical pathway but do not affect activation by the p47phox and amphiphile-independent pathway; (5) Binding of prenylated Rac1 to membrane-mimicking phospholipid vesicles is, nevertheless, enhanced when these contain neg. charged lipids. It is proposed that preferential inhibition of oxidase activation, via the p47phox and amphiphile-independent pathway, is a reflection of interference by the inhibitors with Rac-dependent recruitment of p67phox to the membrane.

REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 2002:569001 CAPLUS

DOCUMENT NUMBER: 137:259237

TITLE: Participation of Rac GTPase Activating Proteins in the Deactivation of the Phagocytic NADPH Oxidase

AUTHOR(S): Moskwa, Patryk; Dagher, Marie-Claire; Paclet, Marie-Helene; Morel, Francoise; Ligeti, Erzsebet

CORPORATE SOURCE: Department of Physiology, Semmelweis University, Budapest, H-1444, Hung.

SOURCE: Biochemistry (2002), 41(34), 10710-10716
CODEN: BICHAW; ISSN: 0006-2960

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of the present study was to investigate possible mechanisms that could be involved in the deactivation of the assembled, catalytically active NADPH oxidase of phagocytic cells and thereby lead to termination of O2•- production Our major findings are the following: (1) Addition of GDP to the active oxidase is able to reduce O2•- production both in the fully purified and in a semirecombinant cell-free activation system. (2) P67phox inhibits GTP hydrolysis on Rac whereas p47phox has no effect on Rac GTPase activity. (3)Soluble regulatory proteins (GTPase activating protein, guanine nucleotide dissociation inhibitor, and the Rac-binding domain of the target protein p21-activated kinase) inhibit activation of the NADPH oxidase but have no effect on electron transfer via the assembled enzyme complex. (4)Membrane-associated GTPase activating proteins (GAPs) have access also to the assembled, catalytically active oxidase. Taken together, we propose that the GTP-bound active form of Rac is required for sustained enzyme activity and that membrane-localized GAPs have a role in the deactivation of NADPH oxidase.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2002:678269 CAPLUS
DOCUMENT NUMBER: 137:215779
TITLE: Inhibitory effects of a dominant-interfering form of the Rho-GTPase Cdc42 in the chemoattractant-elicited signaling pathways leading to NADPH oxidase activation in differentiated HL-60 cells
AUTHOR(S): Rabiet, Marie-Josephe; Tardif, Marianne; Braun, Laurence; Boulay, Francois
CORPORATE SOURCE: Departement Reponse et Dynamique Cellulaires/Biochimie et Biophysique des Systemes Integ=res (Unite Mixte de Recherche 5092 Commissariat a l'Energie Atomique/Centre National de la Recherche Scientifique/Universite Joseph Fourier), Grenoble, F-38054, Fr.
SOURCE: Blood (2002), 100(5), 1835-1844
CODEN: BLOOAW; ISSN: 0006-4971
PUBLISHER: American Society of Hematology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A tetracycline-controlled expression system was adapted to the human promyelocytic HL-60 cell line by placement of the transactivator (tTA-off) sequence under the control of the human EF-1α promoter region. Constitutively active and dominant-inhibitory forms of Cdc42 (Cdc42V12 and Cdc42N17, resp.) were conditionally expressed in this system. The expression of Cdc42V12 had no marked effect on chemoattractant-mediated superoxide production, corroborating previous results indicating that the GTP-bound form of Cdc42 is ineffective in directly activating NADP (NADPH) oxidase in a cell-free system. However, the N17 mutant potently inhibited chemoattractant-induced superoxide production The expression of Cdc42N17 interfered with the GTP-loading of Rac and Ras and with the activation of the MAP-kinase pathway. A drastic reduction of chemoattractant-induced inositol-1,4,5-trisphosphate formation and calcium mobilization was observed, corroborating previous in vitro study results identifying PLCβ2 as a Rac/Cdc42 effector. Cdc42N17 was also found to inhibit the translocation of Ras-GRF2, a guanine nucleotide exchange factor for Ras and Rac but not for Cdc42. Thus, the dominant-inhibitory mutant Cdc42N17 was found to interfere at multiple levels in the signaling pathways. The pleiotropic inhibitory effects of Cdc42N17 illustrate the potential pitfalls of using dominant-inhibitory proteins to study the function of Ras-family GTPases. In this regard, a number of conclusions drawn from the use of dominant-inhibitory mutants in myeloid cells might have to be reconsidered.
REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002313639 EMBASE
TITLE: Cell surface CD4 interferes with the infectivity of HIV-1 particles released from T cells.
AUTHOR: Cortes, Maria Jose; Wong-Staal, Flossie; Lama, Juan (correspondence)
CORPORATE SOURCE: Dept. of Medicine, University of California, San Diego, Mail Code 0665, 9500 Gilman Dr., San Diego, CA 92093-0665, United States. jlama@ucsd.edu
SOURCE: Journal of Biological Chemistry, (18 Jan 2002) Vol. 277, No. 3, pp. 1770-1779.
Refs: 51
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States

DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 2002
Last Updated on STN: 19 Sep 2002

AB The CD4 protein is required for the entry of human immunodeficiency virus (HIV) into target cells. Upon expression of the viral genome, three HIV-1 gene products participate in the removal of the primary viral receptor from the cell surface. To investigate the role of surface-CD4 in HIV replication, we have created a set of Jurkat cell lines which constitutively express surface levels of CD4 comparable to those found in peripheral blood lymphocytes and monocytes. Expression of low levels of CD4 on the surface of producer cells exerted an inhibitory effect on the infectivity of HIV-1 particles, whereas no differences in the amount of cell-free p24 antigen were observed. Higher levels of cell surface CD4 exerted a stronger inhibitory effect on infectivity, and also affected the release of free virus in experiments where the viral genomes were delivered by electrotransfection. The CD4-mediated inhibition of HIV-1 infectivity was not observed in experiments where the vesicular stomatitis virus G protein was used to pseudotype viruses, suggesting that an interaction between CD4 and gp120 is required for interference. In contrast, inhibition of particle release by high levels of cell-surface CD4 was not overcome by pseudotyping HIV-1 with foreign envelope proteins. Protein analysis of viral particles released from HIV-infected Jurkat-T cells revealed a cd4dependent reduction in the incorporation of gp120. These results demonstrate that physiological levels of cell-surface CD4 interfere with HIV-1 replication in T cells by a mechanism that inhibits envelope incorporation into viral membranes, and therefore provide an explanation for the need to down-modulate the viral receptor in infected cells. Our findings have important implications for the spread of HIV in vivo and suggest that the CD4 down-modulation function may be an alternative target for therapeutic intervention.

L4 ANSWER 13 OF 52 EMBASE
ACCESSION NUMBER: 2001323663 EMBASE
TITLE: Ceramide inhibition of mammalian phospholipase D1 and D2 activities is antagonized by phosphatidylinositol 4,5-bisphosphate.
AUTHOR: Singh, I.N.; Stromberg, L.M.; Bourgoin, S.G.; Sciorra, V.A.; Morris, A.J.; Brindley, D.N. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Signal Transduction Research Group, University of Alberta, Edmonton, Alta. T6G 2S2, Canada. david.brindley@ualberta.ca
SOURCE: Biochemistry, (18 Sep 2001) Vol. 40, No. 37, pp. 11227-11233.
Refs: 44
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Oct 2001
Last Updated on STN: 4 Oct 2001

AB Ceramides inhibit phospholipase D (PLD) activity in several mammalian cell types. These effects have been related to preventing activation by ARF1, RhoA, and protein kinase C-α and -β and

therefore indicate that PLD1 is inhibited. In the present work, we investigated the effects of ceramides in inhibiting both PLD1 and PLD2 and the interaction with another activator, phosphatidylinositol 4,5-bisphosphate (PIP(2)). PLD1 and PLD2 were overexpressed separately in Sf9 insect cells using baculovirus vectors. In our cell-free system, PLD1 activity was inhibited completely by C(2)-ceramide at sub-optimum concentrations of PIP(2) (3 and 6 μM), whereas at supra-optimum PIP(2) concentrations (18 and 24 νM) C(2)-ceramide did not inhibit PLD1 activity. Partially purified PLD2 exhibited an absolute requirement for PIP(2) when the activity was measured using Triton X-100 micelles. Ceramides inhibited PLD2 activity, and this inhibition was decreased as PIP(2) concentrations increased. However, C(2)-ceramide also reversibly inhibited the activity of PLD1 and PLD2 mutants in which binding of PIP(2) was decreased, indicating that ceramides are interacting with the catalytic core of the mammalian PLDs. By contrast, C(2)-ceramide failed to produce a significant inhibition of PLDs from bacteria and plants. Our results provide a novel demonstration that ceramides reversibly inhibit mammalian PLD2 as well as PLD1 activities and that both of these actions are more pronounced when PIP(2) concentrations are rate-limiting.

L4 ANSWER 14 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:705492 CAPLUS
DOCUMENT NUMBER: 136:33449
TITLE: A chemical inhibitor of N-WASP reveals a new mechanism for targeting protein interactions
AUTHOR(S): Peterson, Jeffrey R.; Lokey, R. Scott; Mitchison, Timothy J.; Kirschner, Marc W.
CORPORATE SOURCE: Department of Cell Biology and the Institute for Chemistry and Cell Biology, Harvard Medical School, Boston, MA, 02115, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2001), 98(19), 10624-10629
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cell morphol. and motility are governed largely by complex signaling networks that ultimately engage the actin cytoskeleton. Understanding how individual circuits contribute to the process of forming cellular structures would be aided greatly by the availability of specific chemical inhibitors. We have used a novel chemical screen in Xenopus cell-free exts. to identify compds. that inhibit signaling pathways regulating actin polymerization Here we report the results of a high-throughput screen for compds. that inhibit phosphatidylinositol 4,5-bisphosphate (PIP2)-induced actin assembly and the identification of the first compound, a cyclic peptide, known to block actin assembly by inhibiting an upstream signaling component. We identify the target of this compound as N-WASP, a protein that has been investigated for its role as a node interconnecting various actin signaling networks. We show that this compound prevents activation of the Arp2/3 complex by N-WASP by allosterically stabilizing the auto-inhibited conformation of N-WASP.
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2001:628247 CAPLUS
DOCUMENT NUMBER: 135:355107
TITLE: Regulation of Paramecium primaurelia glycosylphosphatidylinositol biosynthesis via dolichol phosphate mannose synthesis

AUTHOR(S): Azzouz, N.; Gerold, P.; Kedees, M. H.; Shams-Eldin, H.; Werner, R.; Capdeville, Y.; Schwarz, R. T.
CORPORATE SOURCE: Zentrum fur Hygiene und Medizinische Mikrobiologie, Philipps-Universitat Marburg, Marburg, 35037, Germany
SOURCE: Biochimie (2001), 83(8), 801-809
CODEN: BICMBE; ISSN: 0300-9084
PUBLISHER: Editions Scientifiques et Medicales Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A set of glycosylinositol-phosphoceramides, belonging to a family of glycosylphosphatidyl-inositols (GPIs) synthesized in a cell-free system prepared from the free-living protozoan Paramecium primaurelia has been described. The final GPI precursor was identified and structurally characterized as: ethanolamine-phosphate-6Manα1-2Manα1-6(mannosylphosphate) Manα1-4glucosamine-inositol-phospho-ceramide. During investigations on the biosynthesis of the acid-labile modification, the addnl. mannosyl phosphate substitution, it was observed that the use of the nucleotide triphosphate analog GTPγS (guanosine 5-O-(thiotriphosphate)) blocks the biosynthesis of the mannosylated GPI glycolipids. GTPγS inhibits the synthesis of dolichol-phosphate-mannose, which is the donor of the mannose residues for GPI biosynthesis. Therefore, the authors investigated the role of GTP binding regulatory 'G' proteins using cholera and pertussis toxins and an intracellular second messenger cAMP analog, 8-bromo-cAMP. The data suggest the involvement of classical heterotrimeric G proteins in the regulation of GPI-anchor biosynthesis through dolichol-phosphate-mannose synthesis via the activation of adenylyl cyclase and protein phosphorylation. Furthermore, the data suggest that GTPγS interferes with synthesis of dolichol monophosphate, indicating that the dolichol kinase is regulated by the heterotrimeric G proteins.
REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 2000:822042 CAPLUS
DOCUMENT NUMBER: 134:111782
TITLE: Inducible membrane recruitment of small GTP-binding proteins by rapamycin-based system in living cells
AUTHOR(S): Castellano, Flavia; Chavrier, Philippe
CORPORATE SOURCE: Institut Curie-Recherche, CNRS UMR 144, Paris, 75248, Fr.
SOURCE: Methods in Enzymology (2000), 325(Regulators and Effectors of Small GTPases, Part D), 285-295
CODEN: MENZAU; ISSN: 0076-6879
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The regulation of actin cytoskeleton dynamics in response to extracellular stimuli is mediated by members of the Rho GTP-binding protein family. Most of the studies analyzing the role of Rho proteins in the regulation of actin reorganization have used either expression of dominant inhibitory or constitutively active Rho proteins on microinjection/transfection into recipient cells or, more recently, have attempted to reconstitute actin filament assembly on the addition of recombinant Rho GTP-binding proteins in cell-free assays. An approach has been developed to induce the translocation of various proteins to the plasma membrane, to activate specific signal transduction pathways, and to induce protein-protein interactions in vivo. This system exploits the ability of certain natural cell-permeable compds. to induce protein dimerization. One such compound, the immunosuppressant rapamycin, binds with high affinity to intracellular receptors comprising the FK506-binding protein family,

including FKBP12. FKBP12-bound rapamycin interacts with another protein called FRAP through its 11-kDa domain called FRB and inhibits the kinase activity of FRAP, resulting in cell cycle arrest. In this tripartite complex, rapamcyin acts as an adaptor to join FKBP to FRB. This system has been modified to permit the controlled and local recruitment of activated Rho proteins to discrete sites underneath the plasma membrane mimicking the activation step of Rho GTP-binding proteins by guanine exchange factors. Chimeric Rho proteins containing the FRB domain have been constructed that, on the addition of rapamycin, are recruited to FKBP domains expressed as the cytoplasmic region of an engineered transmembrane receptor, which includes the extracellular domain of CD25. A further element of this system has been to analyze the effect of the local enrichment of the Rho chimeras at discrete sites of the plasma membrane on FKBP receptor clustering using anti-CD25 antibodies. Using this approach, it was observed that the recruitment of Cdc42 to plasma membrane elicits the formation of actin-based membrane protrusions. The protocols used in these studies are described. (c) 2000 Academic Press.

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 52 EMBASE DUPLICATE 1

ACCESSION NUMBER: 1999222018 EMBASE

TITLE: Amino-terminal cysteine residues of RGS16 are required for palmitoylation and modulation of G(i)- and G(q)-mediated signaling.

AUTHOR: Druey, Kirk M.

CORPORATE SOURCE: Molec. Signal Transduction Section, Laboratory of Allergic Diseases, National Institutes of Health, Bethesda, MD 20852, United States.

AUTHOR: Ugur, Ozlem; Backlund, Peter S.; Jones, Teresa L. Z. (correspondence)

CORPORATE SOURCE: Metabolic Diseases Branch, NIDDK, National Institutes of Health, Bethesda, MD 20892, United States. tlzj@helix.nih.gov

AUTHOR: Caron, Joan M.

CORPORATE SOURCE: Department of Physiology, Univ. of Connecticut Health Center, Farmington, CT 06030, United States.

AUTHOR: Chen, Ching-Kang

CORPORATE SOURCE: Division of Biology, California Institute of Technology, Pasadena, CA 91125, United States.

AUTHOR: Jones, Teresa L. Z. (correspondence)

CORPORATE SOURCE: Bldg. 10, National Institutes of Health, Bethesda, MD 20892-1802, United States. tlzj@helix.nih.gov

AUTHOR: Ugur, Ozlem

CORPORATE SOURCE: Dept. Pharmacol./Clin. Pharmacol., Ankara University Medical School, Sihhiye, 06100 Ankara, Turkey.

SOURCE: Journal of Biological Chemistry, (25 Jun 1999) Vol. 274, No. 26, pp. 18836-18842.
Refs: 55
ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical and Experimental Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 8 Jul 1999
Last Updated on STN: 8 Jul 1999

AB RGS proteins (Regulators of G protein Signaling) are a recently discovered family of proteins that accelerate the GTPase activity of heterotrimeric G protein α subunits of the i, q, and 12 classes. The proteins share a homologous core domain but have divergent amino-terminal sequences that

are the site of palmitoylation for RGS-GAIP and RGS4. We investigated the function of palmitoylation for RGS16, which shares conserved amino-terminal cysteines with RGS4 and RGS5. Mutation of cysteine residues at residues 2 and 12 blocked the incorporation of [(3)H]palmitate into RGS16 in metabolic labeling studies of transfected cells or into purified RGS proteins in a cell-free palmitoylation assay. The purified RGS16 proteins with the cysteine mutations were still able to act as GTPase-activating protein for G(i)α. Inhibition or a decrease in palmitoylation did not significantly change the amount of protein that was membrane-associated. However, palmitoylation-defective RGS16 mutants demonstrated impaired ability to inhibit both G(i)and G(q)-linked signaling pathways when expressed in HEK293T cells. These findings suggest that the amino-terminal region of RGS16 may affect the affinity of these proteins for Gα subunits in vivo or that palmitoylation localizes the RGS protein in close proximity to Gα subunits on cellular membranes.

L4 ANSWER 18 OF 52 EMBASE DUPLICATE 2

ACCESSION NUMBER: 1999322171 EMBASE
TITLE: Aluminum fluoride inhibits phospholipase D activation by a GTP-binding protein-independent mechanism.
AUTHOR: Li, Liang; Fleming, Norman (correspondence)
CORPORATE SOURCE: Department of Oral Biology, Univ. Manitoba, 780 Bannatyne Ave., Winnipeg, Man. R3E 0W2, Canada. nfleming@ms.umanitoba.ca
AUTHOR: Fleming, Norman (correspondence)
CORPORATE SOURCE: Department of Oral Biology, University of Manitoba, 780 Bannatyne Avenue, Winnipeg, Man. R3E 0W2, Canada. nfleming@ms.umanitoba.ca
SOURCE: FEBS Letters, (24 Sep 1999) Vol. 458, No. 3, pp. 419-423. Refs: 40
ISSN: 0014-5793 CODEN: FEBLAL
PUBLISHER IDENT.: S 0014-5793(99)01196-5
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 Oct 1999
Last Updated on STN: 7 Oct 1999

AB Aluminum fluoride (AlF(4)(-)) inhibited guanine nucleotide-activated phospholipase D (PLD) in rat submandibular gland cell-free lysates in a concentration-dependent response. This effect was consistent in permeabilized cells with endogenous phospholipid PLD substrates. Inhibition was not caused by either fluoride or aluminum alone and was reversed by aluminum chelation. Inhibition of PLD by aluminum fluoride was not mediated by cAMP, phosphatases 1, 2A or 2B, or phosphatidate phosphohydrolase. AlF(4)(-) had a similar inhibitory effect on rArf-stimulated PLD, but did not block the translocation of Arf from cytosol to membranes, indicating a post-GTP-binding-protein site of action. Oleate-sensitive PLD, which is not guanine nucleotide-dependent, was also inhibited by AlF(4)(-), supporting a G protein-independent mechanism of action. A submandibular Golgi-enriched membrane preparation had high PLD activity which was also potently inhibited by AlF(4)(-), leading to speculation that the known fluoride inhibition of Golgi vesicle transport may be PLD-mediated. It is proposed that aluminum fluoride inhibits different forms of PLD by a mechanism that is independent of GTP-binding proteins and that acts via a membrane-associated target which may be the enzyme itself. Copyright (C) 1999 Federation of European Biochemical Societies.

L4 ANSWER 19 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1999:476862 CAPLUS
DOCUMENT NUMBER: 131:237949
TITLE: Inhibition by alkylamines of NADPH oxidase through blocking the assembly of enzyme components
AUTHOR(S): Sawai, Tohru; Asada, Makoto; Nishizawa, Yukio; Nunoi, Hiroyuki; Katayama, Kouichi
CORPORATE SOURCE: Department of Drug Discovery, Eisai Tsukuba Research Laboratories, Tsukuba, 300-2635, Japan
SOURCE: Japanese Journal of Pharmacology (1999), 80(3), 237-242
CODEN: JJPAAZ; ISSN: 0021-5198
PUBLISHER: Japanese Pharmacological Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Alkylamines inhibit NADPH oxidase both in intact neutrophils and in a cell-free system. The aim of this study was to examine the mechanism underlying this inhibitory effect. Among alkylamines with different chain lengths, the C12 compound (laurylamine) showed the greatest inhibitory effect on the cell-free NADPH oxidase activity induced by arachidonic acid (AA) in the presence of GTPγS. The inhibition was overcome by further addition of AA, and it was observed irresp. of whether laurylamine was added before or after the enzyme activation by AA. When added prior to the enzyme activation, laurylamine blocked translocation to the membrane of all three cytosolic components (p47-phox, p67-phox and rac) in a cell-free translocation assay. When added after the activation, laurylamine released only rac from the membrane. Laurylamine did not inhibit the reduction of cytochrome c by xanthine oxidase, suggesting that it does not have superoxide-scavenging activity. These results indicate that laurylamine inhibits both the activation process of NADPH oxidase and the activated enzyme itself by blocking the assembly of the oxidase components.
REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 20 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1998236062 EMBASE
TITLE: Brefeldin A inhibits cell-free , de novo synthesis of poliovirus.
AUTHOR: Cuconati, Andrea; Molla, Akhteruzzaman; Wimmer, Eckard (correspondence)
CORPORATE SOURCE: Dept. Molec. Genet. and Microbiol., School of Medicine, State Univ. New York at Stony Brook, Stony Brook, NY 11794, United States. wimmer@asterix.bio.sunysb.edu
AUTHOR: Wimmer, Eckard (correspondence)
CORPORATE SOURCE: Dept. Molec. Genet. and Microbiol., School of Medicine, State Univ. New York at Stony Brook, Stony Brook, NY 11794-5222, United States. wimmer@asterix.bio.sunysb.edu
AUTHOR: Cuconati, Andrea
CORPORATE SOURCE: Ctr. for Adv. Biotech. and Medicine, Rutgers University, Piscataway, NJ 08854-5638, United States.
AUTHOR: Molla, Akhteruzzaman
CORPORATE SOURCE: Abbott Laboratories, Abbott Park, IL 60064-3500, United States.
AUTHOR: Wimmer, Eckard (correspondence)
CORPORATE SOURCE: Dept. of Molec. Genetics/Microbiol., School of Medicine, State University of New York, Stony Brook, NY 11794-5222, United States. wimmer@asterix.bio.sunysb.edu
SOURCE: Journal of Virology, (Aug 1998) Vol. 72, No. 8, pp.

6456-6464.
Refs: 59
ISSN: 0022-538X CODEN: JOVIAM
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology: Bacteriology, Mycology, Parasitology and Virology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 4 Sep 1998
Last Updated on STN: 4 Sep 1998

AB Brefeldin A (BFA), an inhibitor of intracellular vesicle-dependent secretory transport, is a potent inhibitor of poliovirus RNA replication in infected cells. We have determined that the unknown mechanism of BFA inhibition of replication is reproduced in the cell-free poliovirus translation, replication, and encapsidation system. Furthermore, we provide evidence suggesting that the cellular mechanism targeted by BFA, the GTP- dependent synthesis of secretory transport vesicles, may be involved in vital RNA replication in the system via a soluble cellular GTP-binding and - hydrolyzing activity. This activity is related to the ARF (ADP-ribosylation factor) family of GTP-binding proteins. ARFs are required for the formation of several classes of secretory vesicles, and some family members are indirectly inactivated by BFA. Peptides that function as competitive inhibitors of ARF activity in cell-free transport systems also inhibit poliovirus RNA replication, and this inhibitory effect can be countered by the addition of exogenous ARF. We suggest that BFA inhibition of replication is diagnostic of a requirement for ARF activity in the cell-free system.

L4 ANSWER 21 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1998:792341 CAPLUS
DOCUMENT NUMBER: 130:135468
TITLE: Nuclear transport factor p10/NTF2 functions as a Ran-GDP dissociation inhibitor (Ran-GDI)
AUTHOR(S): Yamada, Masami; Tachibana, Taro; Imamoto, Naoko; Yoneda, Yoshihiro
CORPORATE SOURCE: Dep. Anat. Cell Biol., Osaka Univ. Med. Sch., Osaka, 565-0871, Japan
SOURCE: Current Biology (1998), 8(24), 1339-1342
CODEN: CUBLE2; ISSN: 0960-9822
PUBLISHER: Current Biology Publications
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The cytosolic nuclear transport factor p10/NTF2 is required for the translocation of karyophilic mols through nuclear pores [1-3], and the small GTPase Ran is a key regulator of protein transport between the nucleus and cytoplasm [4,5]. It has been reported that p10/NTF2 interacts directly and specifically with Ran-GDP but not with Ran-GTP [6]. The precise role(s) of p10/NTF2 in the Ran GTP/GDP cycle are thus far unclear, however. In this study, we show that mammalian p10NTF2 dramatically inhibits the dissociation of [3H]GDP from Ran and the binding of [35S]GTPγS from Ran following the dissociation of non-radioactive GDP by RCC1, the only known mammalian guanine nucleotide exchange factor for Ran (Ran-GEF) [7]. In contrast, the dissociation of [35S]GTPγS from Ran, which was also catalyzed by RCC1, was not affected by p10/NTF2. Furthermore, the activities of wild-type p10/NTF2 and the mutant forms M84T and D92G in an assay of nuclear protein import in a digitonin-permeabilized cell-free system correlated with their level of inhibition of the dissociation of nucleotide from Ran-GDP.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 22 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 3

ACCESSION NUMBER: 1998093247 EMBASE
TITLE: Corequirement of specific phosphoinositides and small GTP-binding protein Cdc42 in inducing actin assembly in Xenopus egg extracts.
AUTHOR: Ma, Le; Cantley, Lewis C.; Kirschner, Marc W. (correspondence)
CORPORATE SOURCE: Department of Cell Biology, Harvard Medical School, 240 Longwood Avenue, Boston, MA 02115, United States. marc@hms.harvard.edu
AUTHOR: Cantley, Lewis C.
CORPORATE SOURCE: Division of Signal Transduction, Beth Israel Hospital, Boston, MA 02115, United States.
AUTHOR: Janmey, Paul A.
CORPORATE SOURCE: Division of Experimental Medicine, Brigham and Women's Hospital, Boston, MA 02115, United States.
SOURCE: Journal of Cell Biology, (9 Mar 1998) Vol. 140, No. 5, pp. 1125-1136.
Refs: 62
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 7 May 1998
Last Updated on STN: 7 May 1998

AB Both phosphoinositides and small GTP-binding proteins of the Rho family have been postulated to regulate actin assembly in cells. We have reconstituted actin assembly in response to these signals in Xenopus extracts and examined the relationship of these pathways. We have found that GTPγS stimulates actin assembly in the presence of endogenous membrane vesicles in low speed extracts. These membrane vesicles are required, but can be replaced by lipid vesicles prepared from purified phospholipids containing phosphoinositides. Vesicles containing phosphatidylinositol (4,5) bisphosphate or phosphatidylinositol (3,4,5) trisphosphate can induce actin assembly even in the absence of GTPγS. RhoGDI, a guanine-nucleotide dissociation inhibitor for the Rho family, inhibits phosphoinositide-induced actin assembly, suggesting the involvement of the Rho family small G proteins. Using various dominant mutants of these G proteins, we demonstrate the requirement of Cdc42 for phosphoinositide-induced actin assembly. Our results suggest that phosphoinositides may act to facilitate GTP exchange on Cdc42, as well as to anchor Cdc42 and actin nucleation activities. Hence, both phosphoinositides and Cdc42 are required to induce actin assembly in this cell-free system.

L4 ANSWER 23 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1997:749446 CAPLUS
DOCUMENT NUMBER: 128:73256
ORIGINAL REFERENCE NO.: 128:14263a,14266a
TITLE: Ran-unassisted nuclear migration of a 97-kD component of nuclear pore-targeting complex
AUTHOR(S): Kose, Shingo; Imamoto, Naoko; Tachibana, Taro; Shimamoto, Takuya; Yoneda, Yoshihiro
CORPORATE SOURCE: Department of Anatomy and Cell Biology, Osaka University Medical School, Suita, 565, Japan
SOURCE: Journal of Cell Biology (1997), 139(4), 841-849
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press

DOCUMENT TYPE: Journal
LANGUAGE: English
AB A 97-kD component of nuclear pore-targeting complex (the β-subunit of nuclear pore-targeting complex [PTAC]/importin/karyopherin) mediates the import of nuclear localization signal (NLS)-containing proteins by anchoring the NLS receptor protein (the α-subunit of PTAC/importin/karyopherin) to the nuclear pore complex (NPC). The import requires a small GTPase Ran, which interacts directly with the β-subunit. The present study describes an examination of the behavior of the β-subunit in living cells and in digitonin-permeabilized cells. In living cells, cytoplasmically injected β-subunit rapidly migrates into the nucleus. The use of deletion mutants reveals that nuclear migration of the β-subunit requires neither Ran- nor α-subunit-binding but only the NPC-binding domain of this mol., which is also involved in NLS-mediated import. Furthermore, unlike NLS-mediated import, a dominant-neg. Ran, defective in GTP-hydrolysis, did not inhibit nuclear migration of the β-subunit. In the digitonin-permeabilized cell-free import assay, the β-subunit transits rapidly through the NPC into the nucleus in a saturating manner in the absence of exogenous addition of soluble factors. These results show that the β-subunit undergoes translocation at the NPC in a Ran-unassisted manner when it does not carry α-subunit/NLS substrate. Therefore, a requirement for Ran arises only when the β-subunit undergoes a translocation reaction together with the α-subunit/NLS substrate. The results provide an insight to the yet unsolved question regarding the mechanism by which proteins are directionally transported through the NPC, and the role of Ran in this process.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 24 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 1997201338 EMBASE
TITLE: Pathophysiological functions of ATP-sensitive K(+) channels in myocardial ischemia.
AUTHOR: Hiraoka, Masayasu, Dr. (correspondence)
CORPORATE SOURCE: Dept. of Cardiovascular Diseases, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45, Yushima, Bunkyo-ku, Tokyo 113, Japan.
AUTHOR: Hiraoka, Masayasu, Dr. (correspondence)
CORPORATE SOURCE: Department Cardiovascular Diseases, Medical Research Institute, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113, Japan.
SOURCE: Japanese Heart Journal, (1997) Vol. 38, No. 3, pp. 297-315.
Refs: 116
ISSN: 0021-4868 CODEN: JHEJAR
COUNTRY: Japan
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 23 Jul 1997
Last Updated on STN: 23 Jul 1997
AB The ATP-sensitive K(+) channels (K(ATP)) are characterized by strong inhibition by intracellular ATP but their activity is also modulated by various intra- and extracellular factors with complicated and undefined mechanism. These factors include a low concentration of ADP (or ATP/ADP

ratio), a mildly low pH, G-protein coupled process, adenosine and so on. Intracellular ATP has a ligand action to inhibit the channel activity on the one hand, but on the other ATP is necessary for maintaining the channels in an operative state, probably due to the enzymatic process involving ATP hydrolysis. K(ATP) is inhibited by antidiabetic sulfonylureas and sodium 5-hydroxydecanoate. The channels are activated by the K(+) channel openers in an ATP-dependent manner, but may have diverse mechanisms of actions depending on different compounds. The K(ATP) channel openings are responsible for shortening the action potential duration (APD) and partial K(+)-efflux during early ischemia. The discrepancy between the high sensitivity of intracellular ATP to inhibit K(ATP) in cell-free, inside-out patches and millimolar orders of myocardial ATP concentration determined by the biochemical techniques may cast some doubts on the actual openings of this channel. It can be explained by the presence of cofactors to stimulate channel opening, heterogeneity or compartmentation of ATP distribution in the cell, the properties and high density of K(ATP), or a combination of these factors. The opening of K(ATP) during ischemia may contribute to the development and aggravation of serious arrhythmias to some extent, but their opening also protects cellular damage, limits infarct size and improves recovery of cardiac function during reperfusion, acting as a cardioprotection mechanism. K(ATP) opening may mimick the effects of ischemic preconditioning, but its effect may be variable among different animal species and experimental conditions. Further studies are necessary to clarify the actual role of channel opening and the molecular mechanism.

L4 ANSWER 25 OF 52 MEDLINE on STN DUPLICATE 4
ACCESSION NUMBER: 1996199181 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8621595
TITLE: Enhancement of protein kinase C-dependent O2 production in Epstein-Barr virus-transformed B lymphocytes by p120Ras-GAP antisense oligonucleotide.
AUTHOR: Schmid E; Koziol J A; Babior B M
CORPORATE SOURCE: Department of Molecular and Experimental Medicine, The Scripps Research Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: AI-24227 (United States NIAID)
AI-28479 (United States NIAID)
SOURCE: The Journal of biological chemistry, (1996 Apr 19) Vol. 271, No. 16, pp. 9320-5.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 27 Jun 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 18 Jun 1996

AB The mammalian Ras GTPase-activating protein (p120Ras-GAP) interacts with activated members of the Ras superfamily of GTP-binding proteins to accelerate their deactivation by sharply increasing their rates of GTP hydrolysis. Among the Ras-family proteins interacting with p120Ras-GAP is Rap1A/Krev1, whose activity is not affected by p120Ras-GAP but which competes with Ras for p120Ras-GAP. A second protein that interacts with p120Ras-GAP is P190Rac-GAP, which activates the GTPase of guanine nucleotide-binding proteins of the Rho family (including Rac1 and Rac2). Both these p120Ras-GAP-binding proteins are of interest in connection with the regulation of the respiratory burst oxidase, Rap1A/Krev1 because it copurifies with cytochrome b558 and

p190Ras-GAP because it inhibits the Rac2-dependent activation of the respiratory burst oxidase in a cell-free system. Using an 18-mer antisense oligonucleotide, we were able to decrease the expression of p120Ras-GAP in Epstein-Barr virus-transformed B lymphocytes. Under conditions where p120Ras-GAP expression was significantly depressed by antisense oligonucleotides, we observed a 40% increase in protein kinase C-dependent but not receptor-dependent O2 production. In contrast, sense and scrambled oligonucleotides had no effect on either p120Ras-GAP expression or O2 production. Our results suggest a role for p120Ras-GAP as a negative regulator in the protein kinase C-mediated activation of the respiratory burst oxidase.

L4 ANSWER 26 OF 52 EMBASE DUPLICATE 5

ACCESSION NUMBER: 1996041176 EMBASE
TITLE: Cytoplasmic domain of rhodopsin is essential for post-Golgi vesicle formation in a retinal cell-free system.
AUTHOR: Deretic, Dusanka (correspondence); Puleo-Scheppke, Belen; Trippe, Claudia
CORPORATE SOURCE: Department of Pathology, Univ. Texas Hlth. Sci. Ctr. S. A., San Antonio, TX 78284-7750, United States. DERETICD@UTHSCSA.EDU
AUTHOR: Deretic, Dusanka (correspondence)
CORPORATE SOURCE: Dept. of Pathology, Univ. Texas Hlth. Sci. Ctr. S. A., 7703 Floyd Curl Dr., San Antonio, TX 78284-7750, United States. DERETICD@UTHSCSA.EDU
AUTHOR: Deretic, Dusanka (correspondence)
CORPORATE SOURCE: Dept. of Pathology, Univ. of Texas Health Science Center, 7703 Floyd Curl Dr., San Antonio, TX 78284-7750, United States.
SOURCE: Journal of Biological Chemistry, (26 Jan 1996) Vol. 271, No. 4, pp. 2279-2286.
Refs: 43
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 26 Feb 1996
Last Updated on STN: 26 Feb 1996

AB In retinal photoreceptors, highly polarized organization of the light-sensitive organelle, the rod outer segment, is maintained by the sorting of rhodopsin and its associated proteins into distinct post. Golgi vesicles that bud from the trans-Golgi network (TGN) and by their vectorial transport toward the rod outer segment. We have developed an assay that reconstitutes the formation of these vesicles in a retinal cell-free system. Vesicle formation in this cell-free assay is ATP-, GTP-, and cytosol-dependent. In frog retinas vesicle budding also proceeds at 0 °C, both in vivo and in vitro. Vesicles formed in vitro are indistinguishable from the vesicles formed in vivo by their buoyant density, protein composition, topology, and morphology. In addition to the previously identified G-proteins, these vesicles also contain rab11. Concurrently with vesicle budding, resident proteins are retained in the TGN. Collectively these data suggest that rhodopsin and its associated proteins are sorted upon exit from the TGN in this cell-free system. Removal of membrane-bound GTP-binding proteins of the rab family by rab GDP dissociation inhibitor completely abolishes formation of these vesicles and results in the retention of rhodopsin in the Golgi. A monoclonal antibody to the cytoplasmic (carboxyl-terminal) domain of rhodopsin and

its Fab fragments strongly inhibit vesicle formation and arrest newly synthesized rhodopsin in the TGN rather than the Golgi. Therefore rhodopsin sorting at the exit from the TGN is mediated by the interaction of its cytoplasmic domain with the intracellular sorting machinery.

L4 ANSWER 27 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 6

ACCESSION NUMBER: 1996224630 EMBASE
TITLE: In vitro activation of the NADPH oxidase by fluoride. Possible involvement of a factor activating GTP hydrolysis on Pac (Rac-GAP).
AUTHOR: Wolfl, Jutta; Geiszt, Miklos; Ligeti, Erzsebet (correspondence)
CORPORATE SOURCE: Department of Physiology, Semmelweis Medical University, Budapest, Hungary.
AUTHOR: Dagher, Marie-Claire; Fuchs, Alexandra
CORPORATE SOURCE: Laboratoire de Biochimie, Dept. de Biol. Molec. et Structurale, Ctr. d'Etudes Nucleaires de Grenoble, France.
AUTHOR: Ligeti, Erzsebet (correspondence)
CORPORATE SOURCE: Department of Physiology, Semmelweis Medical University, P.O. Box 259, H-1444 Budapest 8, Hungary.
AUTHOR: Ligeti, Erzsebet (correspondence)
CORPORATE SOURCE: Department Physiology, Semmelweis Medical University, P.O. Box 259, H-1444 Budapest, Hungary.
SOURCE: European Journal of Biochemistry, (1996) Vol. 239, No. 2, pp. 369-375.
Refs: 46
ISSN: 0014-2956 CODEN: EJBCAI
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 21 Oct 1996
Last Updated on STN: 21 Oct 1996

AB The possible mechanism of activation of the NADPH oxidase by fluoride was investigated in the cell-free system. It is shown that the stimulatory effect of fluoride is inhibited by guanosine 5'-0-(2-thiodiphosphate) (GDP[S]) and potentiated by GTP. The effect of fluoride is not additive with GTP[S]. Fluoride activation requires the presence of Mg(2+) in millimolar concentration but is independent of Al(3+). The activating effect of fluoride is preserved in solubilized membrane extract after removal of the majority of heterotrimeric GTP-binding proteins by immunoadsorption. Fluoride has no direct action either on the nucleotide exchange or GTP hydrolysis of the isolated Rac protein. In contrast, fluoride effectively inhibits Rac-GTPase activity enhanced by a membrane component. In this way, fluoride could prolong the prevalence of Rac in the GTP-bound state and, as a consequence, activate NADPH oxidase; The possibility of the involvement of a membrane-bound Rac GTPase-activating protein activity in the physiological regulation of the enzyme is raised.

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ACCESSION NUMBER: 1996220933 EMBASE
TITLE: Regulation of receptor-mediated endocytosis by Rho and Rac.
AUTHOR: Lamaze, C.; Chuang, T.-H.; Terlecky, L.J.; Bokoch, G.M.; Schmid, S.L. (correspondence)
CORPORATE SOURCE: Department of Cell Biology, Scripps Research Institute, 10666 N. Torrey Pines Road, San Diego, CA 92037, United States.
SOURCE: Nature, (1996) Vol. 382, No. 6587, pp. 177-179.

ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 14 Aug 1996
Last Updated on STN: 14 Aug 1996

AB PINOCYTOSIS and membrane ruffling are among the earliest and most dramatic cellular responses to stimulation by growth factors or other mitogens. The small Ras-related G proteins Rho and Rac have a regulatory role in membrane ruffling and activated Rho has been shown to stimulate pinocytosis when microinjected into Xenopus oocytes. In contrast to these well established effects of Rho and Rac on plasma membrane morphology and bulk pinocytosis, there has been no evidence for their involvement in the regulation of receptor-mediated endocytosis in clathrin-coated pits. Here we show that activated Rho and Rac inhibit transferrin-receptor-mediated endocytosis when expressed in intact cells. Furthermore, we have reconstituted these effects in a cell-free system and established that Rho and Rac can regulate clathrin-coated vesicle formation.

L4 ANSWER 29 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1997:147833 CAPLUS
DOCUMENT NUMBER: 126:184075
ORIGINAL REFERENCE NO.: 126:35501a,35504a
TITLE: 1-Methyladenine inhibits adenylate cyclase in starfish oocytes
AUTHOR(S): Karaseva, Evgenia; Lamash, Nina; Khotimchenko, Yurij
CORPORATE SOURCE: Laboratory of Cytophysiology and Pharmacology, Institute of Marine Biology, Far East Branch, Russian Academy of Sciences, Vladivostok, 690041, Russia
SOURCE: Invertebrate Reproduction & Development (1996), 30(1-3, Diversity in Invertebrate Reproduction), 153-158
CODEN: IRDEE2; ISSN: 0792-4259
PUBLISHER: Balaban Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of 1-methyladenine (1-MeA) on adenylate cyclase (AC) basal activity and on preliminary stimulated AC activity was investigated in oocyte membrane prepns. of the starfish Aphelasterias japonica. 1-MeA inhibited the membrane-bound AC activity both after its addition to intact oocytes and in cell-free expts. GTP did not affect AC activity but it intensified the inhibitory effect of 1-MeA on AC activity. Sodium fluoride (F-) stimulated the oocyte AC (8 fold), while 1-MeA significantly reduced F--stimulated activity. Manganese ($MnCl_2$, 5 mM) stimulated AC (150 fold), but 1-MeA did not reduce Mn^{2+}-stimulated activity. However, Mn^{2+}-stimulated AC activity was inhibited by 1-MeA in the presence of $MgCl_2$. Forskolin stimulated AC activity (7 fold) and 1-MeA had no effect on AC. Thus, the inhibitory effect of 1-MeA on stimulated AC activity is displayed only after stimulation of the regulatory AC subunit. The authors suggest that 1-MeA inhibits the oocyte AC acting via inhibitory regulatory Gi-protein of AC.

L4 ANSWER 30 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1996:251379 CAPLUS
DOCUMENT NUMBER: 124:310428
ORIGINAL REFERENCE NO.: 124:57375a,57378a
TITLE: A role for ADP-ribosylation factor 1, but not COP I, in secretory vesicle biogenesis from the trans-Golgi network

AUTHOR(S): Barr, Francis A.; Huttner, Wieland B.
CORPORATE SOURCE: Cell Biology Programme, European Molecular Biology Laboratory, Heidelberg, D-69120, Germany
SOURCE: FEBS Letters (1996), 384(1), 65-70
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A synthetic N-myristoylated peptide corresponding to the amino-terminal domain of ADP-ribosylation factor 1 (ARF1) markedly increases, in a cell-free system using post-nuclear supernatant from PC12 cells, the biogenesis of constitutive secretory vesicles and immature secretory granules from the trans-Golgi network (TGN). The related N-myristoylated ARF4 peptide only weakly stimulates, and the non-myristoylated ARF1 and ARF4 peptides inhibit, the biogenesis of these secretory vesicles. In a modified cell-free system using TGN membranes, coatomer-depleted cytosol supports the biogenesis of TGN-derived secretory vesicles to the same extent as control cytosol. These results suggest a role for ARF1, but not the COP I coat, in secretory vesicle biogenesis from the TGN, possibly via the activation of phospholipase D.

L4 ANSWER 31 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:561390 CAPLUS
DOCUMENT NUMBER: 122:306544
ORIGINAL REFERENCE NO.: 122:55533a,55536a
TITLE: Regulation of oxidative burst using low molecular weight, GTP-binding protein-derived peptides and analogs
INVENTOR(S): Bokoch, Gary M.; Curnutte, John T.
PATENT ASSIGNEE(S): Scripps Research Institute, USA
SOURCE: PCT Int. Appl., 96 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9503819	A1	19950209	WO 1994-US8631	19940729
W: AU, CA, FI, JP, NO				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
US 5726155	A	19980310	US 1993-156552	19931115
AU 9474092	A	19950228	AU 1994-74092	19940729
PRIORITY APPLN. INFO.:			US 1993-102944 A	19930802
			US 1993-156552 A	19931115
			WO 1994-US8631 W	19940729

AB The present invention relates to optionally substituted, non-toxic peptides and derivs. capable of inhibiting superoxide production in phagocytic cells. The invention also relates to compns. and methods useful in inhibiting inflammation and in treating inflammatory disorders such as autoimmune disorders, gout, adult respiratory distress syndrome, asthma, myocardial infarction, and various dermatol. disorders. The present invention contemplates compns. derived from low mol. weight GTP-binding proteins (LMWG), mastoparan, GAP proteins, and related peptides. The invention further contemplates compns. useful in inhibiting activation of NADPH oxidase or in promoting GDP/GTP exchange. Therapeutic compns. containing various inhibitors, and methods of making and using same, are also disclosed. Peptides derived from Rac1, Rac2, Rap1A, Rap1B, mastoparan, and ICS4 were shown to inhibit NADPH oxidase in a cell -free system. P190 GAP inhibited human neutrophil NADPH oxidase

activity by stimulating GTP hydrolysis by Rac.

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ACCESSION NUMBER: 1995289450 EMBASE
TITLE: Selective inhibition of ras-dependent cell growth by farnesylthiosalisylic acid.
AUTHOR: Marom, M.; Haklai, R.; Egozi, Y.; Kloog, Y. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, George S. Wise Fac. of Life Sciences, Tel Aviv University, Tel Aviv 699787, Israel.
AUTHOR: Ben-Baruch, G.
CORPORATE SOURCE: Dept. of Obstetrics and Gynecology, Sheba Medical Center, Tel Aviv University, Tel Aviv 699787, Israel.
AUTHOR: Marciano, D.
CORPORATE SOURCE: Israel Inst. for Biological Research, POB 19, Ness Ziona 70450, Israel.
SOURCE: Journal of Biological Chemistry, (22 Sep 1995) Vol. 270, No. 38, pp. 22263-22270.
Refs: 47
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 17 Oct 1995
Last Updated on STN: 17 Oct 1995

AB S-trans,trans-Farnesylthiosalicylic acid (FTS) is a novel farnesylated rigid carboxylic acid derivative. In cell-free systems, it acts as a potent competitive inhibitor (K(i) = 2.6 μM) of the enzyme prenylated protein methyltransferase (PPMTase), which methylates the carboxyl-terminal S- prenylcysteine in a large number of prenylated proteins including Ras. In such systems, FTS inhibits Ras methylation but not Ras farnesylation. Inhibition of the PPMTase by FTS in homogenates or membranes of a variety of tissues and cell lines is inferred from a block in the methylation of exogenously added substrates such as N. acetyl-S-trans,trans-farnesyl-L- cysteine and of endogenous substrates including small GTP-binding proteins. FTS can also inhibit methylation of these proteins in intact cells (e.g. in Rat-1 fibroblasts, Ras-transformed Rat-1, and B16 melanoma cells). Unlike in cell-free systems, however, relatively high concentrations of FTS (50-100 μM) are required for partial blocking (10-40%) of protein methylation in the intact cells. Thus, FTS is a weak inhibitor of methylation in intact cells. Because methylation is the last step in the processing of Ras and related proteins, FTS is not likely to affect steps that precede it, e.g. protein prenylation. This may explain why the growth and gross morphology of a variety of cultured cell types (including Chinese hamster ovary, NIH3T3, Rat1, B16 melanoma, and PC12) is not affected by up to 25 μM FTS and is consistent with the observed lack of FTS-induced cytotoxicity. Nevertheless, FTS reduces the levels of Ras in cell membranes and can inhibit Ras-dependent cell growth in vitro, independently of methylation. It inhibits the growth of human Ha-ras-transformed cells (EJ cells) and reverses their transformed morphology in a dose-dependent manner (0.1-10 μM). The drug does not interfere with the growth of cells transformed by v-Raf or T-antigen but inhibits the growth of ErbB2-transformed cells and blocks the mitogenic effects of epidermal and basic fibroblast growth factors, thus implying its selectivity toward Ras growth signaling, possibly via modulation of Ras-Raf communication. Taken together, the results raise the possibility that FTS may specifically interfere with the interaction of Ras with a farnesylcysteine recognition domain in the cell

membrane. This drug, and perhaps other farnesylated rigid carboxylic acid analogs, may be used for in vitro characterization of the PPMTase and for the identification of a putative Ras farnesylcysteine recognition domain in cell membranes.

L4 ANSWER 33 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:628904 CAPLUS
DOCUMENT NUMBER: 123:50003
ORIGINAL REFERENCE NO.: 123:8835a,8838a
TITLE: Cytosolic ADP-ribosylation factors are not required for endosome-endosome fusion but are necessary for GTPγS inhibition of fusion
AUTHOR(S): Spiro, David J.; Taylor, Timothy C.; Melancon, Paul; Wessling-Resnick, Marianne
CORPORATE SOURCE: Program Biological Biomedical Sci., Harvard Medical Sch., Boston, MA, 02115, USA
SOURCE: Journal of Biological Chemistry (1995), 270(23), 13693-7
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A specific role for ADP-ribosylation factors (ARFs) in in vitro endosome-endosome fusion has been proposed (Lenhard, J. M., et al., 1992). However, in vivo studies have failed to support a function for ARFs in the endocytic pathway, since an antagonist of ARF activities, brefeldin A, does not interfere with receptor internalization (Schonhorn, J. E., and Wessling-Resnick, M., 1994). This controversy surrounding the exact function of ARF in endocytic vesicle traffic prompted us to critically re-examine the involvement of ARFs in cell-free endosome fusion. Cytosol depleted of ARF activity was capable of supporting in vitro endocytic vesicle fusion but failed to support inhibition of this reaction in the presence of guanosine 5'-3-O-(thio)triphosphate (GTPγS). Addition of purified ARF1 restored the ability of the ARF-depleted cytosol to inhibit endosome fusion when incubated with GTPγS. Both endocytic vesicle fusion and the GTPγS-mediated inhibition of vesicle fusion were unaffected by brefeldin A. Moreover, the ATP requirement and kinetics of cell -free fusion are not altered by brefeldin A or depletion of cytosolic ARFs. These results suggest that cytosolic ARFs are not necessary for endosomal vesicle fusion in vitro but are responsible for inhibition of fusion in the presence of GTPγS and cytosolic factors in a brefeldin A-resistant manner.

L4 ANSWER 34 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1995:492660 CAPLUS
DOCUMENT NUMBER: 122:233537
ORIGINAL REFERENCE NO.: 122:42519a,42522a
TITLE: Regulation of Cdc2/cyclin B activation by Ran, a Ras-related GTPase
AUTHOR(S): Clarke, Paul R.; Klebe, Christian; Wittinghofer, Alfred; Karsenti, Eric
CORPORATE SOURCE: Cell Biology Programme, European Molecular Biology Laboratory, Heidelberg, 69117, Germany
SOURCE: Journal of Cell Science (1995), 108(3), 1217-25
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB During the cell cycle, a checkpoint prevents the initiation of mitosis until S-phase is completed. The mol. mechanism may involve the RCC1

protein, which catalyzes guanine nucleotide exchange on the Ras-related nuclear protein, Ran (or TC4). Genetic studies have suggested that RCC1 may be involved in sensing the replication state of DNA and controlling the activation of Cdc2/cyclin B protein kinase through Ran. In this report, we present direct biochem. evidence for the post-translational control of Cdc2/cyclin B activation by Ran. In a cell-free system of concentrated Xenopus egg exts. supplemented with nuclei, a mutant form of Ran (T24N) analogous to dominant inactive mutants of other Ras-related GTPases inhibits Cdc2/cyclin B activation in the presence of replicating nuclear DNA. This role for Ran is mediated through control of the tyrosine phosphorylation state of Cdc2 and appears to be distinct from other effects on nuclear import, nuclear formation and DNA replication. When exts. were supplemented with RCC1 protein prior to addition of Ran T24N, inhibition of Cdc2/cyclin B by Ran T24N was relieved. This suggests that Ran T24N may act in a dominant manner by sequestering RCC1 in an inactive form. In contrast to Ran T24N, a mutant of Ran (Q69L) defective in GTPase activity and hence locked in the GTP-bound state has no inhibitory effect on Cdc2/cyclin B activation. In the light of these results, we propose that generation of the GTP-bound form of Ran is required for Cdc2/cyclin B activation and entry into mitosis when this process is coupled to the progression of S-phase.

L4 ANSWER 35 OF 52 EMBASE

ACCESSION NUMBER: 1996009520 EMBASE
TITLE: Zn(2+) depletion blocks endosome fusion.
AUTHOR: Aballay, A.; Sarrouf, M.N.; Colombo, M.I.; Stahl, P.D.; Mayorga, L.S. (correspondence)
CORPORATE SOURCE: Institute Histologia y Embriologia, Casilla de corree 56, 5500 Mendoza, Argentina.
SOURCE: Biochemical Journal, (1995) Vol. 312, No. 3, pp. 919-923. ISSN: 0264-6021 CODEN: BIJOAK
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jan 1996
Last Updated on STN: 27 Jan 1996

AB Fusion among endosomes is an important step for transport and sorting of internalized macromolecules. Working in a cell-free system, we previously reported that endosome fusion requires cytosol and ATP, and is sensitive to N-ethylmaleimide. Fusion is regulated by monomeric and heterotrimeric GTP-binding proteins. We now report that fusion can proceed at very low Ca(2+) concentrations, i.e. < 30 nM, Moreover, fusion is not affected when intravesicular Ca(2+) is depleted by preincubation of vesicles with calcium ionophores (5 μM ionomycin or A23187) in the presence of calcium chelators (5 mM EGTA or 60 mM EDTA). The results indicate that fusion can proceed at extremely low concentrations of intravesicular and extravesicular Ca(2+). However, BAPTA [1,2-bis-(o-aminophenoxy)ethane-N,N,N',N'-tetra-acetic acid], a relatively specific Ca(2+) chelator, inhibits fusion. BAPTA binds other metals besides Ca(2+). We present evidence that BAPTA inhibition is due not to Ca(2+) chelation but to Zn(2+) depletion. TPEN [N,N,N',N'-tetrakis-(2-pyridylmethyl) ethylenediamine], another metal-ion chelator with low affinity for Ca(2+), also inhibited fusion. TPEN- and BAPTA-inhibited fusions were restored by addition of Zn(2+). Zn(2+)-dependent fusion presents the same characteristics as control fusion. In intact cells, TPEN inhibited transport along the endocytic pathway. The results indicate that Zn(2+) depletion blocks endosome fusion, suggesting that this ion is necessary for the function of one or more factors involved in the fusion process.

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ACCESSION NUMBER: 1995251306 EMBASE
TITLE: Inhibition of Rac function using antisense oligonucleotides.
AUTHOR: Dorseuil, O. (correspondence); Leca, G.; Vazquez, A.; Gacon, G.
CORPORATE SOURCE: Inst. Cochin Genetique Moleculaire, INSERM Unite 257, 75014 Paris, France.
SOURCE: Methods in Enzymology, (1995) Vol. 256, pp. 358-366. ISSN: 0076-6879 CODEN: MENZAU
COUNTRY: United States
DOCUMENT TYPE: Journal; General Review; (Review)
FILE SEGMENT: 026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 19 Sep 1995
Last Updated on STN: 19 Sep 1995

AB Using a Rac antisense oligonucleotide we were able, in a whole cell system, to decrease the Rac protein content and to inhibit superoxide production. Previous studies done in cell-free systems suggested the involvement of Rac proteins in NADPH oxidase activation. This chapter provided evidence that Rac is implicated not only in superoxide production from cell-free systems but also in an intact cell system. This chapter also showed that the Rac dependency of the NADPH oxidase exists not only in phagocytic cells but also in B lymphocytes. We observed a clear correlation between the decrease of the Rac protein content and the inhibition of superoxide production, thus demonstrating the physiological involvement of Rac proteins in the NADPH oxidase activity of B lymphocytes.

L4 ANSWER 37 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1995:802105 CAPLUS
DOCUMENT NUMBER: 123:224165
ORIGINAL REFERENCE NO.: 123:39895a,39898a
TITLE: Sorting and budding of constitutive secretory vesicles in hepatocytes and hepatoma cells
AUTHOR(S): Barthel, Andreas; Nickel, Walter; Tonko, Cristiane; Soling, Hans-Dieter
CORPORATE SOURCE: Department of Clinical Biochemistry, Universitat Goettingen, Goettingen, 37075, Germany
SOURCE: Advances in Enzyme Regulation (1995), 35, 283-92 CODEN: AEZRA2; ISSN: 0065-2571
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A population of post-trans Golgi network (post-TGN) secretory vesicles were isolated from hepatocytes. The vesicles were 100-150 nm in diameter, and carried heparan sulfate proteoglycans. Secretory proteins (albumin, apolipoprotein E, fibrinogen) were sorted into different post-TGN secretory vesicles. A member of the ARF family of small GTP-binding proteins is associated with there vesicles. A unique peripheral membrane protein of these vesicles (VAPP14) exist also on the TGN. Brefeldin A leads to a dissociation of VAPP14 from the TGN. Antibodies against VAPP14 inhibit budding of proteoglycans containing vesicles from the TGN in a cell-free system. Inhibition occurred also in the presence of GTPγS. The same type of vesicles exist in H35 Reuber hepatoma cells.

L4 ANSWER 38 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 1994:693117 CAPLUS
DOCUMENT NUMBER: 121:293117
ORIGINAL REFERENCE NO.: 121:53379a,53382a
TITLE: Inhibition of protein farnesyltransferase: a possible mechanism of tumor prevention by dehydroepiandrosterone sulfate
AUTHOR(S): Schulz, Stefan; Nyce, Jonathan W.
CORPORATE SOURCE: Dep. Mol. Pharmacol. Therapeutics, East Carolina Univ., Greenville, NC, 27834, USA
SOURCE: Carcinogenesis (1994), 15(11), 2649-52
CODEN: CRNGDP; ISSN: 0143-3334
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Dehydroepiandrosterone sulfate (DHEAS) is the most abundant adrenal steroid with apparent anticarcinogenic properties. Given the authors recent observation of the dehydroepiandrosterone-mediated inhibition of protein isoprenylation and the fact that 99% of the circulating dehydroepiandrosterone is sulfated, with less than 1% representing the free steroid, the authors investigated the effects of DHEAS on post-translational isoprenylation of proteins. The authors here report that exposure of HT-29 SF human colonic adenocarcinoma cells to DHEAS inhibited the incorporation of [3H]mevalonate into cellular proteins in a dose-dependent manner when endogenous mevalonate synthesis was blocked by lovastatin. Interestingly, significant inhibition was observed at concns. of DHEAS which are comparable to peak serum levels of this steroid occurring in the second decade of life. Immunopptn. revealed that isoprenylation of p21ras was also suppressed in DHEAS-treated HT-29 SF cells. In a cell-free system, DHEAS inhibited the farnesylation of a biotinylated decapeptide corresponding to the C-terminus of K-ras by 50% at a concentration of 100 μM. This suggests that DHEAS inhibits isoprenylation of cellular proteins, including p21ras, at a point in the mevalonate pathway distal to 3-hydroxy-3-methylglutaryl-CoA reductase and that the DHEAS-mediated suppression of protein farnesylation may largely be due to inhibition at the level of protein farnesyltransferase. Thus, these findings may provide a plausible explanation for the antitumor activity of DHEAS.

ACCESSION NUMBER: 1995013577 EMBASE
TITLE: The G protein-activating peptide, mastoparan, and the synthetic NH(2)- terminal ARF peptide, ARFp13, inhibit in vitro Golgi transport by irreversibly damaging membranes.
AUTHOR: Weidman, P.J. (correspondence); Winter, W.M.
CORPORATE SOURCE: Biochemistry/Molecular Biology Dept., St. Louis University Medical School, 1402 S. Grand Blvd., St. Louis, MO 63104, United States.
SOURCE: Journal of Cell Biology, (1994) Vol. 127, No. 6 II, pp. 1815-1827.
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 1 Feb 1995
Last Updated on STN: 1 Feb 1995

AB Mastoparan is a cationic amphipathetic peptide that activates trimeric G proteins, and increases binding of the coat protein β-COP to Golgi membranes. ARFp13 is a cationic amphipathic peptide that is a putative

specific inhibitor of ARF function, and inhibits coat protein binding to Golgi membranes. Using a combination of high resolution, three-dimensional electron microscopy and cell-free Golgi transport assays, we show that both of these peptides inhibit in vitro Golgi transport, not by interfering in the normal functioning of GTP-binding proteins, but by damaging membranes. Inhibition of transport is correlated with inhibition of nucleotide sugar uptake and protein glycosylation, a decrease in the fraction of Golgi cisternae exhibiting normal morphology, and a decrease in the density of Golgi-coated buds and vesicles. At peptide concentrations near the IC(50) for transport, those cisternae with apparently normal morphology had a higher steady state level of coated buds and vesicles. Kinetic analysis suggests that this increase in density was due to a decrease in the rate of vesicle fission. Pertussis toxin treatment of the membranes appeared to increase the rate of vesicle formation, but did not prevent the membrane damage induced by mastoparan. We conclude that ARFp13 is not a specific inhibitor of ARF function, as originally proposed, and that surface active peptides, such as mastoparan, have the potential for introducing artifacts that complicate the analysis of trimeric G protein involvement in regulation of Golgi vesicle dynamics.

L4 ANSWER 40 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1994:550776 CAPLUS
DOCUMENT NUMBER: 121:150776
ORIGINAL REFERENCE NO.: 121:27105a,27108a
TITLE: Inhibition of endocytic transport by aluminum fluoride implicates GTPases as regulators of endocytosis
AUTHOR(S): Colombo, Maria I.; Lenhard, James; Mayorga, Luis; Beron, Walter; Hall, Heather; Stahl, Philip D.
CORPORATE SOURCE: Sch. Med., Washington Univ., St Louis, MO, 63110, USA
SOURCE: Molecular Membrane Biology (1994), 11(2), 93-100
CODEN: MMEBE7; ISSN: 0968-7688
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The authors' results indicate that AlF inhibits fusion of early endosomes with an intracellular proteolytic compartment. Using the mixing of sequentially internalized ligands as a measure of endocytosis, the authors found that AlF inhibited endocytic transport as assessed by both biochem. and morphol. methods. Taken together these results suggest that AlF affects membrane fusion, a common step in vesicular transport. To further examine the effects of AlF the authors tested this compound in a cell-free assay that reconstitutes fusion among endosomes. AlF affected endosomal fusion in a different way than did GTPγS, an agent that activates both trimeric and small GTPases. The authors' results suggest that the coordinated activation of both classes of GTPases are required for efficient endocytic transport.

L4 ANSWER 41 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 7
ACCESSION NUMBER: 1994014478 EMBASE
TITLE: Regulation of NADPH oxidase activity by Rac GTPase activating protein(s).
AUTHOR: Heyworth, P.G.; Knaus, U.G.; Settleman, J.; Curnutte, J.T.; Bokoch, G.M. (correspondence)
CORPORATE SOURCE: Dept. of Immunology and Cell Biology, Scripps Research Institute, San Diego, CA 92037, United States.
SOURCE: Molecular Biology of the Cell, (1993) Vol. 4, No. 11, pp. 1217-1223.
ISSN: 1059-1524 CODEN: MBCEEV
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry

LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 1994
Last Updated on STN: 30 Jan 1994

AB Activation of the NADPH oxidase of phagocytic cells requires the action of Rac2 or Rac1, members of the Ras superfamily of GTP-binding proteins. Rac proteins are active when in the GTP-bound form and can be regulated by a variety of proteins that modulate the exchange of GDP for GTP and/or GTP hydrolysis. The p190 Rac GTPase Activating Protein (GAP) inhibits human neutrophil NADPH oxidase activity in a cell-free assay system with a K(1) of 100 nM. Inhibition by p190 was prevented by GTPγS, a nonhydrolyzable analogue of GTP. Similar inhibition was seen with a second protein exhibiting Rac GAP activity, CDC42Hs GAP. The effect of p190 on superoxide (O(2)(-)) formation was reversed by the addition of a constitutively GTP-bound Rac2 mutant or Rac1-GTPγS but not by RhoA-GTPγS. Addition of p190 to an activated oxidase produced no inhibitory effect, suggesting either that p190 no longer has access to Rac in the assembled oxidase or that Rac-GTP is not required for activity once O(2)(-) generation has been initiated. These data confirm the role of Rac in NADPH oxidase regulation and support the view that it is the GTP form of Rac that is necessary for oxidase activation. Finally, they raise the possibility that NADPH oxidase may be regulated by the action of GAPs for Rac proteins.

L4 ANSWER 42 OF 52 EMBASE
ACCESSION NUMBER: 1994011940 EMBASE
TITLE: Initiation of RVD response in human platelets: Mechanical-biochemical transduction involves pertussis-toxin-sensitive G protein and phospholipase A(2).
AUTHOR: Margalit, A.; Livne, A.A.; Funder, J.; Granot, Y. (correspondence)
CORPORATE SOURCE: Department of Life Sciences, Ben-Gurion University of the Negev, Beer-Sheva, Israel.
SOURCE: Journal of Membrane Biology, (1993) Vol. 136, No. 3, pp. 303-311.
ISSN: 0022-2631 CODEN: JMBBBO
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 025 Hematology
029 Clinical and Experimental Biochemistry
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 30 Jan 1994
Last Updated on STN: 30 Jan 1994

AB Platelets revert hypotonic-induced swelling by the process of regulatory volume decrease (RVD). We have recently shown that this process is under the control of endogenous hepoxilin A(3). In this work, we investigated the mechanical-biochemical transduction that leads to hepoxilin A(3) formation. We demonstrate that this process is mediated by pertussis-toxin-sensitive G protein, which activates Ca(2+)-insensitive phospholipase A(2), and the sequential release of arachidonic acid. This conclusion is supported by the following observations: (i) RVD response is blocked selectively by the phospholipase A(2) inhibitors manoalide and bromophenacyl-bromide (0.2 and 5 μM, respectively) but not by phospholipase C inhibitors. The addition of arachidonic acid overcame this inhibition; (ii) extracellular Ca(2+) depletion by EGTA (up to 10 mM) does not affect RVD; (iii) intracellular Ca(2+) depletion by BAPTA-AM (100 μM) inhibits RVD but not hepoxilin A(3) formation, as tested by the RVD reconstitution assay; (iv) RVD is inhibited by the G-protein inhibitors, GDP(β)S (1 μM) and pertussis toxin (1 ng/ml). This

inhibition is overcome by addition of arachidonic acid or hypotonic cell-free eluate that contains hepoxilin A(3); (v) NaF, 1 mM, induces hepoxilin A(3) formation, tested by the RVD reconstitution assay; and (vii) GDF(β)S inhibits hepoxilin A(3) formation associated with flow. Therefore, it seems that G proteins are involved in the initial step of the mechanical-biochemical transduction leading to hepoxilin A(3) formation in human platelets.

L4 ANSWER 43 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 8

ACCESSION NUMBER: 1992311935 EMBASE
TITLE: Epidermal cell differentiation inhibitor ADP-ribosylates small GTP-binding proteins and induces hyperplasia of epidermis.
AUTHOR: Sugai, M. (correspondence); Hashimoto, K.; Kikuchi, A.; Inoue, S.; Okumura, H.; Matsumoto, K.; Goto, Y.; Ohgai, H.; Moriishi, K.; Syuto, B.; Yoshikawa, K.; Suginaka, H.; Takai, Y.
CORPORATE SOURCE: Dept. of Microbiology, Uniformed Services Hlth. Sci. Univ., 4301 Jones Bridge Rd., Bethesda, MD 20814-4799, United States.
SOURCE: Journal of Biological Chemistry, (1992) Vol. 267, No. 4, pp. 2600-2604.
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 8 Nov 1992
Last Updated on STN: 8 Nov 1992

AB Epidermal cell differentiation inhibitor (EDIN) is a recently discovered protein which inhibits terminal differentiation of cultured keratinocytes (Sugai, M., Enomoto, T., Hashimoto, K., Matsumoto, K., Matsuo, Y., Ohgai, H., Hong, Y.-M., Inoue, S., Yoshikawa, K., and Suginaka, H. (1990) Biochem. Biophys. Res. Commun. 173, 92-98). The amino acid sequence deduced from the EDIN gene has revealed that EDIN shares high amino acid sequence homology with the exoenzyme C3 of Clostridium botulinum (Inoue, S., Sugai, M., Murooka, Y., Paik, S.-Y., Hong, Y.-M., Ohgai, H., and Suginaka, H. (1991) Biochem. Biophys. Res. Commun. 174, 459-464), which has been shown to ADP- ribosylate the rho/rac proteins (members of the small GTP-binding protein family). We show here that EDIN ADP-ribosylates rhoB p21 in time- and dose- dependent manners in a cell-free system. Kinetic studies of the ADP-ribosylation and peptide mapping of the reaction products of rhoB p21 by EDIN and C3 suggest that the mode of action of the ADP-ribosylation by EDIN is quite similar to that by C3 and that the ADP-ribosylation site of rhoB p21 by EDIN is presumably the same as that by C3. Proteins in epidermal membranes and keratinocyte homogenate with M(r) values of about 22,000 are ADP- ribosylated by EDIN or C3. Treatment of cultured human keratinocytes by EDIN or C3 results in an inhibition of terminal differentiation and a stimulation of growth of the cells. Moreover, EDIN and C3 injected into adult mouse skin induce hyperplasia of epidermis. These results suggest that EDIN and C3 affect growth and differentiation of keratinocytes by ADP-ribosylation of protein(s) with a M(r) of about 22,000, which may be the rho/rac proteins or related proteins.

L4 ANSWER 44 OF 52 MEDLINE on STN DUPLICATE 9

ACCESSION NUMBER: 1992378682 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1324680
TITLE: Molsidomine inhibits the chemoattractant-induced respiratory burst in human neutrophils via a no-independent

mechanism.
AUTHOR: Ervens J; Seifert R
CORPORATE SOURCE: Institut fur Pharmakologie, Freie Universitat Berlin, Germany.
SOURCE: Biochemical pharmacology, (1992 Aug 18) Vol. 44, No. 4, pp. 637-44.
Journal code: 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199209
ENTRY DATE: Entered STN: 9 Oct 1992
Last Updated on STN: 3 Mar 2000
Entered Medline: 21 Sep 1992

AB 3-Morpholino-sydnonimine (SIN-1) is a NO-releasing compound which mimics the effects of cGMP through activation of soluble guanylyl cyclase. Its prodrug, molsidomine (SIN-10), does not release NO but does modulate various cell functions. These findings prompted us to study the effects of SIN-10 and SIN-1 on the respiratory burst in human neutrophils. SIN-10 was more effective than SIN-1 in inhibiting superoxide anion (O2-) formation induced by N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMet-Leu-Phe) and by C5a. The effects of SIN-1 and SIN-10 on O2- formation were additive or less than additive, indicating the sydnonimines acted through a common mechanism. The sydnonimines showed no effect on O2- formations induced by gamma-hexachlorocyclohexane, arachidonic acid and a phorbol ester. They did not inhibit O2- formation induced by xanthine oxidase, by autoxidation of pyrogallol and in a cell -free system from HL-60 leukemic cells. Neutrophils did not convert SIN-10 to SIN-1 as assessed by O2 consumption which accompanies NO release from SIN-1. The cell-permeant analogue of cGMP, N2,2'-O-dibutyryl guanosine 3':5'-monophosphate (Bt2cGMP), and SIN-10 but not SIN-1 inhibited fMet-Leu-Phe-induced O2 consumption. SIN-1 and SIN-10 slightly enhanced agonist binding to formyl peptide receptors, whereas Bt2cGMP was inhibitory. The sydnonimines did not affect GTP hydrolysis of heterotrimeric regulatory guanine nucleotide-binding proteins in HL-60 membranes. SIN-1 but not SIN-10 stimulated ADP-ribosylation of a 39-kDa protein in the cytosol of HL-60 cells. SIN-10 reduced fMet-Leu-Phe-induced rises in cytosolic Ca2+ concentration in neutrophils. These data suggest that SIN-10 inhibits the respiratory burst via a NO-independent mechanism which may involve inhibition of rises in cytosolic Ca2+ concentration.

L4 ANSWER 45 OF 52 EMBASE
ACCESSION NUMBER: 1992220314 EMBASE
TITLE: Biscoclaurine alkaloids inhibit receptor-mediated phospholipase A(2) activation probably through uncoupling of a GTP-binding protein from the enzyme in rat peritoneal mast cells.
AUTHOR: Akiba, S.; Kato, E.; Sato, T., Dr. (correspondence); Fujii, T.
CORPORATE SOURCE: Department of Biochemistry, Kyoto Pharmaceutical University, Yamashina-ku, Kyoto 607, Japan.
SOURCE: Biochemical Pharmacology, (1992) Vol. 44, No. 1, pp. 45-50.
ISSN: 0006-2952 CODEN: BCPCA6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 023 Nuclear Medicine
026 Immunology, Serology and Transplantation
029 Clinical and Experimental Biochemistry

030 Clinical and Experimental Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Aug 1992
Last Updated on STN: 16 Aug 1992

AB The mechanism underlying the inhibitory effect of biscoclaurine (bisbenzylisoquinoline) alkaloids on phospholipase A(2) activation in the signalling system of stimulated rat peritoneal mast cells was studied. Cepharanthine, berbamine and isotetrandrine inhibited antigen- and compound 48/80induced arachidonic acid liberation. but not diacylglycerol formation or histamine release. They had no effect on A23187-induced arachidonic acid liberation, which was prevented by p-bromophenacyl bromide, a known phospholipase A(2) inhibitor, and also did not affect phospholipase A(2) activity in a cell-free system including an exogenous phospholipid substrate. Each alkaloid also inhibited arachidonic acid liberation induced by guanosine 5'-O-(3-thiotriphosphate) in saponin-permeabilized mast cells, and by mastoparan or NaF plus AlCl(3) in intact cells. Furthermore, each alkaloid abolished the inhibitory effect of islet-activating protein on the compound 48/80-induced arachidonic acid liberation. These data suggest that these alkaloids suppress the receptor-mediated phospholipase A(2) activation through, at least in part, uncoupling of a GTP-binding protein from the enzyme, rather than by affecting the enzyme directly.

L4 ANSWER 46 OF 52 EMBASE
ACCESSION NUMBER: 1991212462 EMBASE
TITLE: Enhancement of the actions of smg p21 GDP/GTP exchange protein by the protein kinase A-catalyzed phosphorylation of smg p21.
AUTHOR: Hata, Y.; Kaibuchi, K.; Kawamura, S.; Hiroyoshi, M.; Shirataki, H.; Takai, Y. (correspondence)
CORPORATE SOURCE: Department of Biochemistry, Kobe University, School of Medicine, Kobe 650, Japan.
SOURCE: Journal of Biological Chemistry, (1991) Vol. 266, No. 10, pp. 6571-6577.
ISSN: 0021-9258 CODEN: JBCHA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English
ENTRY DATE: Entered STN: 16 Dec 1991
Last Updated on STN: 16 Dec 1991

AB We have previously shown that cyclic AMP-dependent protein kinase (protein kinase A) phosphorylates smg p21A and -B, ras p21-like small GTP-binding proteins. In the present study, we investigated the function(s) of this phosphorylation by use of the smg p21B purified from human platelets. smg p21B bound to plasma membranes and the protein kinase A-catalyzed phosphorylation of smg p21B reduced this binding. Moreover, the phosphorylation of smg p21B enhanced the two actions of its specific GDP/GTP exchange protein, named GDP dissociation stimulator, when tested in a cell-free system: one is the action to stimulate the GDP/GTP exchange reaction of smg p21B, and the other is the action to inhibit the binding of smg p21B to membranes. Consistently, smg p21B was translocated from the membranes to the cytoplasm when it was phosphorylated by protein kinase A in intact platelets in response to prostaglandin E(1) or dibutyryl cyclic AMP. The protein kinase A-catalyzed phosphorylation of smg p21B affected neither its basal GDP/GTP exchange reaction, basal GTPase activity, nor the GTPase activity stimulated by its specific GTPase activating protein. On the other hand,

we have recently clarified that the structure of the C-terminal region of the post-translationally processed human platelet smg p21B is Lys-Lys-Ser-Ser-all-trans-geranylgeranyl Cys(181) methyl ester, and that this modification of the C-terminal region is essential for smg p21B to bind to membranes. We furthermore determined here that protein kinase A phosphorylated Ser(179) in this C-terminal region of smg p21B. These results indicate that protein kinase A-catalyzed phosphorylation of smg p21B makes smg p21B sensitive to the actions of smg p21 GDP dissociation stimulator.

L4 ANSWER 47 OF 52 MEDLINE on STN DUPLICATE 10
ACCESSION NUMBER: 1991201826 MEDLINE
DOCUMENT NUMBER: PubMed ID: 1849937
TITLE: Activation of human neutrophils by Mycobacterium tuberculosis-derived sulfolipid-1.
AUTHOR: Zhang L; English D; Andersen B R
CORPORATE SOURCE: Department of Medicine and Microbiology/Immunology, University of Illinois, College of Medicine, Chicago.
CONTRACT NUMBER: AI-25656 (United States NIAID)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1991 Apr 15) Vol. 146, No. 8, pp. 2730-6.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: (IN VITRO)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199105
ENTRY DATE: Entered STN: 7 Jun 1991
Last Updated on STN: 18 Dec 2002
Entered Medline: 21 May 1991

AB The principal sulfatide of a group of acidic lipids from virulent Mycobacterium tuberculosis, sulfolipid-1 (SL-1), stimulates neutrophil superoxide (O2-) generation and, at lower concentrations, primes neutrophil response to several other metabolic agonists including FMLP, and PMA. These responses to SL-1 were examined in relation to diacylglycerol (DAG) generation, Ca2+ availability and activation of guanine nucleotide binding proteins
to clarify the signal transduction pathways involved. Pertussis toxin inhibited the ability of SL-1 to both stimulate neutrophils directly and to prime neutrophils for subsequent responses induced by PMA, suggesting a role for one or more guanine nucleotide regulating proteins in both responses. SL-1 induced a rise in neutrophil DAG levels. DAG generation was inhibited by pretreatment of cells with pertussis toxin. Depletion of extracellular Ca2+ ablated O2- release induced by stimulatory levels of SL-1 but did not inhibit the priming effect induced by substimulatory concentrations of the lipid. Investigation of the activation of the neutrophil NADPH oxidase in a cell-
free system revealed that the SL-1-priming effect was associated with translocation of the soluble cytosolic factors required for activation of the enzyme. Cytosolic factor translocation was not observed in pertussis toxin pretreated cells. Our results provide evidence for the role of a guanine nucleotide binding
protein in both priming and direct activation of neutrophils by SL-1. This G protein regulates both SL-1-induced DAG generation and cytosolic cofactor translocation involved in neutrophil activation and priming. The multiplicity of effects of SL-1 on signal transduction pathways leading to phagocyte activation and priming may exert a profound influence on the pathogenicity of M. tuberculosis.

L4 ANSWER 48 OF 52 CAPLUS COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 1991:426615 CAPLUS
DOCUMENT NUMBER: 115:26615
ORIGINAL REFERENCE NO.: 115:4641a,4644a
TITLE: Effects of mastoparan and related peptides on phosphoinositide breakdown in HL-60 cells and cell-free preparations
AUTHOR(S): Gusovsky, Fabian; Soergel, David G.; Daly, John W.
CORPORATE SOURCE: Lab. Bioorg. Chem., Natl. Inst. Health, Bethesda, MD, 20892, USA
SOURCE: European Journal of Pharmacology, Molecular Pharmacology Section (1991), 206(4), 309-14
CODEN: EJPPET; ISSN: 0922-4106
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In differentiated HL-60 cells the amphiphilic peptide mastoparan induces a dose-dependent stimulation of phosphoinositide breakdown with an EC50 value of 9 μM. Such stimulation can be markedly reduced by pretreatment of the cells with pertussis toxin (100 ng/mL, 2 h). In membranes obtained from differentiated HL-60 cells, guanine nucleotides stimulate the formation of inositol phosphates IP2 and IP3. Calcium ions also induce phosphoinositide breakdown in this preparation independent of the presence of guanine nucleotides. In HL-60 cell membranes, mastoparan inhibited GTPγS-stimulation of phosphoinositide breakdown with an IC50 value of 3 μM. Such inhibitory activity of mastoparan also was present in membranes from cells pretreated with pertussis toxin. The calcium-induced stimulation of phosphoinositide breakdown was not inhibited by mastoparan. The analogs mastoparan-X and polistes mastoparan had similar inhibitory activity, whereas the analog des-Ile1-Asn2-mastoparan was inactive. In permeabilized HL-60 cells, mastoparan also inhibited phosphoinositide breakdown. Another amphiphilic peptide, melittin, was inactive in HL-60 intact cells, but like mastoparan it inhibited guanine nucleotide-induced phosphoinositide breakdown in HL-60 cell membranes and permeabilized cells. Thus, mastoparan peptides can stimulate phosphoinositide breakdown in intact HL-60 cells, probably through interactions with a guanine nucleotide binding protein. In permeabilized cells and in cell membranes, mastoparan inhibits guanine nucleotide-mediated phosphoinositide breakdown presumably through an interaction with an intracellular site. The inhibitory action of mastoparan and melittin is probably related to the amphiphilic character of these peptides.

L4 ANSWER 49 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN DUPLICATE 11
ACCESSION NUMBER: 1992003804 EMBASE
TITLE: Trimeric G-proteins of the trans-golgi network are involved in the formation of constitutive secretory vesicles and immature secretory granules.
AUTHOR: Barr, F.A.; Leyte, A.; Mollner, S.; Pfeuffer, T.; Tooze, S.A.; Huttner, W.B. (correspondence)
CORPORATE SOURCE: Cell Biology Programme, European Molecular Biology Laboratory, Postfach 10.2209, D-6900 Heidelberg, Germany.
AUTHOR: Huttner, W.B. (correspondence)
CORPORATE SOURCE: Institute for Neurobiology, University of Heidelberg, Im Neuenheimer Feld 364, D-6900 Heidelberg, Germany.
SOURCE: FEBS Letters, (1991) Vol. 294, No. 3, pp. 239-243.
ISSN: 0014-5793 CODEN: FEBLAL
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 029 Clinical and Experimental Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

ENTRY DATE: Entered STN: 16 Mar 1992
Last Updated on STN: 16 Mar 1992

AB Non-hydrolysable analogues of GTP, such as GTPγS and GMP-PNP, have previously been shown to inhibit the formation of constitutive secretory vesicles (CSVs) and immature secretory granules (ISGs) from the trans-Golgi network (TGN). Using a cell-free system, we show here that the formation of these vesicles is also inhibited by [AlF(4)](-), a compound known to act on trimeric G-proteins. Addition of highly purified G-protein βγ subunits stimulated, in a differential manner, the cell-free formation of both CSVs and ISGs. ADP-ribosylation experiments revealed the presence of a pertussis toxin-sensitive G-protein α subunit in the TGN. We conclude that trimeric G-proteins regulate the formation of secretory vesicles from the TGN.

L4 ANSWER 50 OF 52 MEDLINE on STN DUPLICATE 12

ACCESSION NUMBER: 1991056086 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2173705
TITLE: Preferential inhibition of the platelet-derived growth factor receptor tyrosine kinase by staurosporine.
AUTHOR: Secrist J P; Sehgal I; Powis G; Abraham R T
CORPORATE SOURCE: Department of Pharmacology, Mayo Foundation, Rochester, Minnesota 55905.
CONTRACT NUMBER: CA 42286 (United States NCI)
SOURCE: The Journal of biological chemistry, (1990 Nov 25) Vol. 265, No. 33, pp. 20394-400.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199012
ENTRY DATE: Entered STN: 22 Feb 1991
Last Updated on STN: 3 Mar 2000
Entered Medline: 28 Dec 1990

AB Ligand stimulation of the platelet-derived growth factor receptor (PDGF-R) results in rapid activation of the receptor tyrosine kinase, stimulation of phosphoinositide hydrolysis, an increase in intracellular free Ca2+ concentration ([Ca2+]i), and, ultimately, cellular proliferation. In a previous study, we demonstrated that staurosporine, a known inhibitor of protein kinase C, blocked PDGF-induced [Ca2+]i increases in Swiss mouse 3T3 fibroblasts by a mechanism that appeared unrelated to inhibition of protein kinase activity (Olsen, R., Melder, D., Seewald, M., Abraham, R., and Powis, G. (1990) Biochem. Pharmacol. 39, 968-972). In the present study, we report that staurosporine inhibits ligand-dependent PDGF-R tyrosine kinase activation in cell-free receptor preparations and in intact Swiss 3T3 cells. At the same concentrations (10(-8)-10(-6) M), staurosporine suppressed both the tyrosine phosphorylation of phospholipase C activity and the hydrolysis of phosphoinositides induced by PDGF stimulation of intact cells. In contrast, guanine nucleotide-binding protein-dependent phospholipase C activation induced by bradykinin or fluoroaluminate anion was relatively insensitive to staurosporine. A preferential inhibitory effect of staurosporine on signal generation by the PDGF-R was indicated by findings that epidermal growth factor receptor (EGF-R) tyrosine kinase activity and EGF-dependent phospholipase C in A-431 carcinoma cells were approximately 100-fold less sensitive to this drug. These data indicate that submicromolar concentrations of staurosporine inhibit PDGF-dependent phosphoinositide hydrolysis and Ca2+ mobilization through a proximal inhibitory effect on

ligand-induced activation of the PDGF-R tyrosine kinase.

L4 ANSWER 51 OF 52 EMBASE COPYRIGHT (c) 2008 Elsevier B.V. All rights reserved on STN

ACCESSION NUMBER: 1990269660 EMBASE
TITLE: Exocytosis in mast cells by basic secretagogues: Evidence for direct activation of GTP-binding proteins.
AUTHOR: Aridor, M.; Traub, L.M.; Sagi-Eisenberg, R., Dr. (correspondence)
CORPORATE SOURCE: Dept. Chemical Immunology, The Weizmann Inst. of Science, Rehovot 76100, Israel.
SOURCE: Journal of Cell Biology, (1990) Vol. 111, No. 3, pp. 909-917.
ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
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AB Histamine release induced by the introduction of a nonhydrolyzable analogue of GTP, GTP-γ-S, into ATP-permeabilized mast cells, is associated with phosphoinositide breakdown, as evidenced by the production of phosphatidic acid (PA) in a neomycin-sensitive process. The dependency of both PA formation and histamine secretion on GTP-γ-S concentrations is bell shaped. Whereas concentrations of up to 0.1 mM GTP-γ-S stimulate both processes, at higher concentrations the cells' responsiveness is inhibited. At a concentration of 1 mM, GTP-γ-S self- inhibits both PA formation and histamine secretion. Inhibition of secretion can, however, be overcome by the basic secretagogues compound 48/80 and mastoparan that in suboptimal dose synergize with 1 mM GTP-γ-S to potentiate secretion. Secretion under these conditions is not accompanied by PA formation and is resistant both to depletion of Ca(2+) from internal stores and to pertussis toxin (PtX) treatment. In addition, 48/80, like mastoparan, is capable of directly stimulating the GTPase activity of G-proteins in a cell -free system. Together, our results are consistent with a model in which the continuous activation of a phosphoinositide-hydrolyzing phospholipase C (PLC) by a stimulatory G-protein suffices to trigger histamine secretion. Basic secretagogues of mast cells, such as compound 48/80 and mastoparan, are capable of inducing secretion in a mechanism that bypasses PLC by directly activating a G-protein that is presumably located downstream from PLC (G(E)). Thereby, these secretagogues induce histamine secretion in a receptor-independent manner.

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AB The mechanism by which the β-adrenergic agonist isoproterenol (ISO) modulates voltage-dependent cardiac Na(+) currents (I(Na)) was studied in single ventricular myocytes of neonatal rat using the gigaseal patch-clamp technique. ISO inhibited I(Na) reversibly, making the effect readily distinguishable from the monotonic disease of I(Na) caused by the shift in gating that customarily occurs during whole cell patch-clamp experiments (E. Fenwick, A. Marty, and E. Neher, J. Physiol. Lond. 331: 599-635, 1982; and J.M. Fernandez, A.P. Fox, and S. Krasne, J. Physiol. Lond. 356: 565-585, 1984). The inhibition was biphasic, having fast and slow components, and was voltage-dependent, being more pronounced at depolarized potentials. In whole cell experiments the membrane-permeable adenosine 3',5'-cyclic monophosphate (cAMP) congener 8-bromo-cAMP reduced I(Na). In cell-free inside-out patches with ISO present in the pipette, guanosine 5'-triphosphate (GTP) applied to the inner side of the membrane patch inhibited single Na(+) channel activity. This inhibition could be partly reversed by hyperpolarizing prepulses. The nonhydrolyzable GTP analogue guanosine-5'-O-(3-thiotriphosphate) greatly reduced the probability of single Na(+) channel currents in a Mg(2+)-dependent manner. We propose that ISO inhibits cardiac Na(+) channels via the guanine nucleotide binding, signal-transducing G protein that acts through both direct (membrane delimited) and indirect (cytoplasmic) pathways.

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